PEDIATRIC BLOOD TRANSFUSIONS: BENCHMARKING TOOLS FOR TRANSFUSIONS IN SURGICAL PATIENTS AND THE USE OF CLINICAL DECISION SUPPORT TO OPTIMIZE BLOOD UTILIZATION

by
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ABSTRACT

In recent years, the use of blood products has come under increased scrutiny in an effort to optimize the use of medical resources. We assembled a working group and developed a set of evidence based recommendations for red blood cell (RBC) transfusions at the Johns Hopkins Bloomberg Children's Center (JHBCC). Before implementing the guidelines, we began our studies by using a national surgical dataset to develop regression models that allow for benchmarking of transfusion practices in surgical patients between hospitals (Chapter 1). We then characterized the allocation of RBC to specific high-risk surgeries and found that more than half of the transfusions in children's surgery are associated to only two procedures: spinal fusion for arthrodesis and craniectomy for craniosynostosis (Chapter 2).

Once our guidelines were finalized, we embedded them into a clinical decision support (CDS) logic within our computerized provider ordering system. This intervention reminded providers of the evidence-based guidelines when attempting to transfuse outside of recommended thresholds. We analyzed the effect of the CDS mechanism by comparing incidence rates of transfusion (Chapter 3). We used a zero-inflated negative binomial regression model to adjust for covariates while using historical controls. The CDS intervention was associated with a decrease of blood transfusions in patients >3 months of age (IRR 0.818, $p<0.001$) but not in patients <3 months (IRR 0.972, $p=0.739$).

The ascertainment of pre and post-transfusion hemoglobin values during the year of the intervention allowed us to investigate adherence to the newly created JHBCC guidelines

(Chapter 4). From 1955 transfusions, 41.6% were compliant with institutional recommendations (46.7% in patients <3 months and 35.1% in patients >3 months). Lastly, we studied the different approaches that hospital units have in relation to volume of RBC ordered. While there are differences in comorbidity profiles of patients between hospitals units, we found that similar patients are transfused different volumes depending on where they are admitted to.

These analyses and their results are unique as they describe sophisticated methods and interventions that can serve pediatric practitioners be better informed and improve the use of RBCs in children.

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SUMMARY

Several studies have shown a high variability in transfusion practices in pediatric hospitals. This variability is likely explained in part by varying patient populations and procedures being performed. Therefore an accurate method of comparing blood utilization between centers becomes vital.

Data from the National Surgical Quality Improvement Program-Pediatric from 2012 to 2015 were used. Patients were stratified in two age groups (0-3 months and 3 months to 18 years) We used a forward-stepwise logistic regression approach and developed a model for each age group with data from 2012 and 2014. The models were validated with data from 2013 and 2015. The model for patients <3 months included 18 variables and had excellent discriminatory performance (area under the curve 0.866). The model for patients >3 months to 18 years had 21 variables and an area under the curve of 0.916. In conclusion, multiple preoperative factors have been built into a risk-adjusted model for blood utilization that can be used for benchmarking transfusion rates among hospitals.

INTRODUCTION

Several studies have shown a high variability in transfusion practices in pediatric hospitals.[1–3] This variability is likely explained in part by varying patient populations and procedures being performed. Therefore an accurate method of comparing blood utilization between centers becomes vital. The models put forth in this study can provide such a method by allowing calculation of an observed-to-expected frequency of transfusion from the factors shown here to be significant.

METHODS

Data Source

Data from the American College of Surgeons (ACS) National Surgical Quality Improvement Project – Pediatric (NSQIP-P) Participant Use Data Files (PUFs) from 2012 to 2015 were utilized for this analysis. As stated in the previous chapter, the PUFs contain information on 30-day outcomes on pediatric surgical patients from more than 100 hospitals in the United States, two in Australia, and one in the United Arab Emirates. Pediatric patients were defined as 0 to 18 years of age. A transfusion was defined as an occurrence in which the patient received packed red blood cells, whole blood, or autologous blood transfusion from the surgery start time until 72 hours after. Transfusions received before surgery start time or other blood products (e.g. fresh frozen plasma, platelets, etc.) were not included. The term perioperative transfusion is used for

intraoperative and postoperative transfusions, and the perioperative period is defined as a 72 hour window by NSQIP.

Patients were stratified by perioperative transfusion status (transfused vs. not transfused) and compared according to demographic and clinical characteristics (sex, age category, race/ethnicity, surgical specialty, prematurity, number and day of transfusion occurrence) using chi-square tests. Age was grouped into 4 categories: 0-3 months, 3 months-1 year, 1-10 years, ≥10 years. Race/ethnicity was categorized as White, Black, Asian, Hispanic, American Indian, Pacific Islander and Unknown. Specialty is a defined variable by NSQIP-P based on the operating surgeon.

Model Development and Validation

To develop an adjustment model for transfusion, a forward-stepwise logistic regression analysis was performed using data from the 2012 and 2014 PUFs. The significance level for variable addition was set at 0.05. Due to the significant differences among comorbidities and types of surgeries, two different models were designed, one for patient 0-3 months of age and another one for 3 months to 18 years of age. All preoperative variables available in NSQIP were tested for model construction, with the exception of variables that were not available for all the PUFs studied (e.g. laparoscopic/open approach was not available for 2012, and dialysis was discontinued in 2015) and non-relevant variables for the 0-3 month age group (e.g. cystic fibrosis, diabetes). The final models included 30 variables for 0-3 months of age and 34 variables for ≥3 months of age.

The analysis for patients 0-3 months of age included 30 potential preoperative variables: ventilator dependence, bronchopulmonary dysplasia/chronic lung disease, oxygen requirement, tracheostomy, structural pulmonary/airway abnormalities, cardiac risk factors (factor), previous cardiac surgery, developmental delay/impaired cognitive status, seizure disorder, cerebral palsy, neuromuscular disorder, IVH grade (factor), steroid use within 30 days, nutritional support, systemic inflammatory response syndrome/sepsis/septic shock, inotropic use, prior cardiopulmonary resuscitation, congenital malformation (factor- no; yes neonate 1500g at time of surgery; yes- neonate ≥1500g at time of surgery or patient with history of congenital defect at time of surgery), preoperative transfusion within 48 hours, sex, inpatient/outpatient status, race (factor), ASA (American Society of Anesthesiologists) class (factor), surgical specialty (factor), prematurity (factor), hematologic disorder, malignancy (factor- no cancer; history of; current), open wound, transfer status (factor), esophageal/gastric/intestinal disease.

For the ≥3 months of age model, 34 initial variables were analyzed for potential inclusion into the model: the same variables as the model for 0-3 months plus diabetes (factor- no; insulin dependent; non-insulin dependent), asthma, cystic fibrosis, age category (factor- 3 months to 1 year; 1 year to 10 years; ≥10 years). Correlation between variables was investigated by displaying a correlation matrix. The models built using 2012 and 2014 data were validated using the 2013 and 2015 PUF. The area under a receiver operating characteristics (ROC) curve (AUC) was calculated for each model to test discrimination performance. The Hosmer-Lemeshow test was calculated to assess goodness of fit using the number of covariates of the final model plus one to define the groups. Statistical analysis was performed using Stata 15 (College Station, TX).

RESULTS

A total of 369,176 surgeries were utilized for analysis. Perioperative transfusions occurred in 21,410 (5.8%) of cases (Table 1.1). Female patients were transfused more frequently than males (7.3% vs 4.7%, $p<0.001$). Patients 0 to 3 months of age were transfused more frequently (8.96%) than older patients (3mo-1year, 6.7%; 1-10 years 2.5%; ≥10years 8.1%, $p<0.001$). Black race was associated with a higher proportion of transfusions (7.6%, $p<0.001$). The surgical specialty with the highest proportion of transfused cases was Orthopedic Surgery (15.4%, $p<0.001$). General Surgery had a transfusion occurrence in 4.3% of the cases. The combination of spine cases (extracted from Orthopedic Surgery and Neurosurgery) had a transfusion rate of 41.2%. For patients less than three months of age, prematurity was significantly associated with a transfusion requirement (24.8% vs. 6.3%, $p<0.001$). The majority of cases that were transfused required only 1 transfusion (98.3%) in the perioperative period. 82.4% of transfusions occurred on the day of surgery.

The forward stepwise regression analyses yielded an 18-variable model for patients 0-3 months of age. The variables for the 0-3 month model were (in order of forward selection): ventilator dependence, ASA class, prematurity, preoperative transfusion, SIRS/sepsis/septic shock, malignancy, nutritional support, surgical specialty, hematologic disorder, inpatient status, inotropic support, IVH grade, transfer/origin status, prior CPR, oxygen support, steroid use, sex and race. The variables with the largest association with transfusion were malignancy (current malignancy OR 15.67 [95%CI 7.90-31.08], history of cancer OR 34.11 [3.29-353.66]), ASA

Table 1.1 Population Characteristics by Transfusion Status

	Transfused, n(%)	Not transfused, n(%)	*p*
Sex			
Female	11,576 (7.3)	147,824 (92.7)	
Male	9,834 (4.7)	199,942 (95.3)	<0.001
Age categories			
0-3 months	3,758(11.4)	29,329 (88.6)	
3 months to 1 year	2,988 (6.7)	41,446 (93.3)	
1 to 10 years	3,987 (2.5)	155,609 (97.5)	
≥10 years	10,677 (8.1)	121,382 (91.9)	<0.001
Race/Ethnicity			
White	12,624 (5.8)	207,071 (94.3)	
Black	3,612 (7.6)	43,755 (92.4)	
Asian	639 (4.7)	10,637 (95.3)	
Hispanic	1,834 (4.5)	38,881 (95.5)	
American Indian	85 (5.5)	1,463 (94.5)	
Pacific Islander	65 (4.8)	1,291 (95.2)	
Unknown	2,662 (5.6)	44,668 (94.4)	<0.001
Specialty			
General	6,105 (4.3)	137,073 (95.7)	
Orthopedic	10,762 (15.4)	59,013 (84.6)	
Urology	236 (0.6)	40,689 (99.4)	
Neuro	2,468 (7.1)	32,329 (92.9)	
ENT	220 (0.5)	45,934 (99.5)	
Plastic	1,603 (4.8)	31,892 (95.2)	
Gynecology	16 (1.9)	836 (98.1)	
Spine *	9,722 (41.2)	13,856 (58.8)	<0.001
Premature (if <3months)			
No	1,500 (6.3)	22,472 (93.7)	
Yes	2,258 (24.8)	6,857 (75.2)	<0.001
n of transfusions			
1	21,052 (98.3)	-	
2	305 (1.4)	-	
≥3	53 (0.04)	-	na
Postop day of transfusion			
0	17,633 (82.4)	-	
1	2,092 (9.8)	-	
2	1,207 (5.6)	-	
≥3	458 (2.1)	-	na

(Table 1.1 cont)
ENT, ears, nose and throat. * Spine is a subset of CPT codes taken from Neuro and Orthopedic surgery. na, not applicable.

class (class 4 OR 11.91 [6.50-21.80], class 5 OR 12.00 [5.53-26.03]), surgical specialty (orthopedic OR 3.36 [1.73-6.50], plastic OR 4.42 [2.66-7.34]) and prematurity (25-26 weeks of gestational age OR 4.12 [2.94-5.79]). The AUC on the developing model was 0.8723, and the AUC was 0.8655 on the validation dataset. The Hosmer-Lemeshow goodness-of-fit test had a $p<0.001$ (Table 1.2).

The final model for patients >3 months of age included 21 variables (in order of forward selection): neuromuscular disorder, inpatient status, surgical specialty ASA class, age category, transfer/origin status, malignancy, hematologic disorder, inotropic support, sex, SIRS/sepsis/septic shock, cerebral palsy, preoperative transfusion, congenital malformation, nutritional support, race, cardiac risk factors, oxygen support, tracheostomy, IVH grade and steroid use. The variables with the largest association with transfusion were ASA class (class 5 OR 27.19 [95%CI 12.64-58.49], class 4 OR 6.29 [5.20-7.60]), surgical specialty (orthopedic OR 17.44 [15.71-19.37], plastic OR 5.22 [4.55-5.99]) and inpatient status (OR 16.49 [14.45-18.82]). The AUC on the developing model was 0.9189, and the AUC was 0.9163 on the validation dataset. The Hosmer-Lemeshow goodness-of-fit test p value was <0.001 (Table 1.3). None of the variables in either model had a correlation matrix value >0.5.

Table 1.2 Logistic regression model for transfusion outcome. Patients 0-3 months of age.

Variable	OR	SE	z	P	[95% CI]
Ventilator Dependance	1.57	0.16	4.5	<0.001	[1.29-1.91]
ASA Classification					
2	2.73	0.82	3.33	0.001	[1.51-4.94]
3	6.02	1.81	5.95	<0.001	[3.33-10.86]
4	11.91	3.67	8.03	<0.001	[6.50-21.80]
5	12.00	4.74	6.29	<0.001	[5.53-26.03]
Prematurity (wga)					
35 to 36	1.14	0.14	1.12	0.263	[0.91- 1.44]
33 to 34	1.58	0.22	3.35	0.001	[1.21-2.07]
31 to 32	2.21	0.36	4.85	<0.001	[1.61-3.05]
29 to 30	2.42	0.43	4.97	<0.001	[1.71-3.42]
27 to 28	2.82	0.47	6.19	<0.001	[2.03-3.92]
25 to 26	4.12	0.71	8.21	<0.001	[2.94-5.79]
24	2.05	0.51	2.88	0.004	[1.26-3.34]
<24	3.38	1.06	3.88	<0.001	[1.83-6.26]
Preoperative Transfusion	1.97	0.23	5.92	<0.001	[1.58-2.47]
Preoperative Sepsis/SIRS/Shock					
SIRS	1.71	0.45	2.01	0.045	[1.01-2.87]
Sepsis	3.41	0.64	6.58	<0.001	[2.37-4.91]
Septic Shock	2.44	0.69	3.12	0.002	[1.39-4.26]
Malignancy					
Current	15.67	5.48	7.87	<0.001	[7.90-31.08]
History of cancer	34.11	40.70	2.96	0.003	[3.29-353.66]
Nutritional Support	1.68	0.14	6.24	<0.001	[1.43-1.98]
Surgical Specialty (ref. General)					
Orthopedic	3.36	1.13	3.59	<0.001	[1.73-6.50]
Urology	1.35	0.37	1.08	0.28	[0.78-2.31]
Neuro	1.02	0.13	0.15	0.878	[0.79-1.32]
ENT	0.22	0.08	-4.31	<0.001	[0.11-0.44]
Plastic	4.42	1.14	5.73	<0.001	[2.66-7.34]
Hematologic Disorder	1.74	0.17	5.53	<0.001	[1.43-2.11]
Inpatient status (ref. outpatient)	3.92	1.13	4.75	<0.001	[2.23-6.89]
Inotropic Support	1.48	0.22	2.6	0.009	[1.10-1.98]
IVH grade					
1	1.49	0.33	1.84	0.065	[0.97-2.29]
2	0.53	0.15	-2.27	0.023	[0.30-0.92]

3	0.63	0.17	-1.74	0.082	[0.38-1.06]
4	0.58	0.13	-2.43	0.015	[037-0.90]
Unknown	0.37	0.15	-2.39	0.017	[0.17-0.84]
Transfer/Origin status (ref. admitted from home)					
Admitted through ER	0.61	0.08	-3.65	<0.001	[0.47-0.79]
Outside Hospital	0.83	0.08	-2.01	0.045	[0.69-1.00]
Other	0.76	0.10	-2.03	0.042	[058-0.99]
Prior CPR	1.83	0.44	2.5	0.012	[1.14-2.94]
Oxygen support	1.25	0.12	2.39	0.017	[1.04-1.49]
Steroid use	1.41	0.20	2.45	0.014	[1.07-1.86]
Female (ref. male)	1.19	0.09	2.41	0.016	[1.03-1.38]
Race/Ethnicity (ref. white)					
Black	1.37	0.14	3.16	0.002	[1.13-1.66]
Asian	0.83	0.21	-0.75	0.454	[0.50-1.36]
Hispanic	1.03	0.14	0.2	0.845	[0.78-1.34]
American Indian	1.00	0.49	0.01	0.994	[0.39-2.60]
Pacific Islander	2.20	1.39	1.24	0.214	[0.63-7.62]
Unknown	0.96	0.10	-0.41	0.685	[0.78-1.18]
# observations: 10,864					
# transfusions: 1,263 (11.6%)					
AUC: 0.8723					
HL-value: 25.23 (p<0.001)					

ASA, American Society of Anesthesiologists; wga, weeks of gestational age; SIRS, systemic inflammatory response syndrome; ER, emergency room; IVH, intraventricular hemorrhage; ENT, ears, nose and throat; CPR, cardiopulmonary resuscitation.

DISCUSSION

This study used a large national dataset to develop risk-adjusted models for transfusion use. We identified multiple patient characteristics, outside of the type of procedure, that were strongly associated with transfusion use and should be accounted for when benchmarking transfusion occurrences among hospitals.

Table 1.3 Logistic Regression Model for Transfusion Outcome. Patients ≥3 Months of Age

Variable	OR	SE	z	P	[95% CI]
Neuromuscular Disorder	1.38	0.07	6.45	<0.001	[1.25-1.52]
Inpatient status (ref. outpatient)	16.49	1.11	41.59	<0.001	[14.45-18.82]
Surgical Specialty (ref. General)					
Orthopedic	17.44	0.93	53.56	<0.001	[15.71-19.37]
Urology	0.53	0.07	-4.64	<0.001	[0.41-0.70]
Neuro	2.20	0.13	13.06	<0.001	[1.95-2.47]
ENT	0.22	0.04	-7.66	<0.001	[0.15-0.32]
Plastic	5.22	0.37	23.63	<0.001	[4.55-5.99]
Gyn	1.23	0.53	0.47	0.637	[0.53-2.86]
ASA Classification					
2	1.72	0.08	11.27	<0.001	[1.56-1.89]
3	2.66	0.15	17.32	<0.001	[2.38-2.97]
4	6.29	0.61	19.00	<0.001	[5.20-7.60]
5	27.19	10.63	8.45	<0.001	[12.64-58.49]
Age Categories (ref. 3mo -1 year)					
1-10 years	0.25	0.01	-25.54	<0.001	[0.22-0.27]
≥10 years	0.62	0.03	-9.02	<0.001	[0.55-0.68]
Transfer/Origin status (ref. admitted from home)					
Admitted through ER	0.27	0.02	-22.54	<0.001	[0.24-0.30]
Rehabilitation Facility	0.73	0.26	-0.88	0.378	[0.37-1.46]
Outside Hospital	0.87	0.08	-1.49	0.136	[0.73-1.04]
Other	2.00	0.24	5.75	<0.001	[1.58-2.53]
Malignancy					
Current Cancer	4.34	0.30	21.07	<0.001	[3.79-4.98]
Past History of Cancer	0.73	0.13	-1.78	0.075	[0.52-1.03]
Hematologic Disorder	2.64	0.18	14.05	<0.001	[2.31-3.02]
Inotropic Support	4.62	0.63	11.26	<0.001	[3.54-6.04]
Female (ref. male)	1.37	0.04	9.81	<0.001	[1.28-1.45]
Preoperative Sepsis/SIRS/Shock					
SIRS	1.49	0.20	2.99	0.003	[1.15-1.94]
Sepsis	2.19	0.28	6.13	<0.001	[1.70-2.82]
Septic Shock	4.63	1.31	5.41	<0.001	[2.66-8.06]
Cerebral Palsy	0.66	0.04	-6.67	<0.001	[0.58-0.75]
Preoperative Transfusion	1.88	0.22	5.38	<0.001	[1.50-2.37]
Congenital Malformation	1.23	0.04	5.82	<0.001	[1.15-1.32]
Nutritional Support	1.36	0.08	5.27	<0.001	[1.21-1.52]
Race					

Black	0.97	0.04	-0.57	0.570	[0.89-1.07]
Asian	0.62	0.07	-4.36	<0.001	[0.50-0.77]
Hispanic	0.88	0.05	-2.20	0.028	[0.78-0.99]
American Indian	1.19	0.27	0.75	0.451	[0.76-1.87]
Pacific Islander	0.89	0.30	-0.34	0.735	[0.46-1.73]
Unknown	0.81	0.04	-4.00	<0.001	[0.73-0.90]
Cardiac Risk Factors					
Minor	0.77	0.05	-3.90	<0.001	[0.67-0.88]
Major	0.84	0.07	-2.10	0.036	[0.71-0.99]
Severe	0.66	0.11	-2.63	0.008	[0.48-0.90]
Oxygen Support	1.44	0.12	4.28	<0.001	[1.22-1.70]
Presence of tracheostomy	0.64	0.07	-3.84	<0.001	[0.51-0.80]
IVH grade					
1	1.65	0.36	2.28	0.023	[1.07-2.53]
2	1.07	0.29	0.24	0.810	[0.62-1.83]
3	0.64	0.17	-1.65	0.098	[0.37-1.09]
4	0.52	0.11	-3.07	0.002	[0.34-0.79]
5	0.80	0.15	-1.20	0.229	[0.55-1.15]
Steroid use	1.23	0.10	2.60	0.009	[1.05-1.43]
# records: 108,676					
# transfusions: 5,842 (5.4%)					
AUC: 0.9189					
HL-chi2: 60.94 (*p<0.001*)					

ASA, American Societa of Anesthesiologists; SIRS, systemic inflammatory response syndrome; ER, emergency room; IVH, intraventricular hemorrhage; ENT, ears, nose and throat.

Stey et.al. published a model for non-neonate pediatric surgical patients using NSQIP-P data.[1] Their methodology is similar to the one utilized by the ACS when reporting outcomes to participating institutions. Unfortunately, these hierarchical methods cannot be universally utilized by the participating hospitals because variables such as hospital IDs and CPT outcome-specific risk are not included in the PUF. Notably, the logistic regression models in the present study were instead built only with variables that are available to other centers. Utilizing only these variables, the models still maintained excellent statistical performance. The AUC for the

model in the validation set for the 0-3 months group was 0.867 and in the >3 months group was 0.916. The goodness-of-fit test showed poor calibration of the data, but this finding is very common when using large datasets where minimal differences in observed to expected occurrences have a big impact in the statistical significance of the test.[4]

Premature neonates are at high risk of requiring blood transfusions, and their physiology and dynamic definition of anemia has made them difficult to study. In the study by Stey and associates, patients younger than 28 days were excluded from the study because of their differing physiology and surgical profile compared to other pediatric patients. The present work contributes a model specifically for patients younger than 3 months of age. The magnitude of the variables association with transfusion is significantly different and variables like ventilator dependence, prematurity and prior CPR became increasingly relevant when examining patients <3 months of age compared to older children.

NSQIP-P provides risk-adjusted outcome reports to participating centers in a semi-annual basis. The individual outcome of a perioperative transfusion is not reported; instead it is bundled with other morbidity (e.g. pneumonia, reintubation, pulmonary embolism, etc.) and defined as a composite outcome. In 2018, transfusions began to be reported as an individual occurrence but just for the CPT codes related to spinal fusion. Therefore, the only way of studying risk-adjusted models of transfusion is by analyzing the PUF.

Centers with access to the PUF can follow similar regression techniques and create models for benchmarking specific outcomes of interest and CPT codes. Maizlin and colleagues utilized

NSQIP-P data to develop a predictive model for pediatric wound infections.[5] Bartz-Kuricky and associates created a model to study the effect of cardiac risk factors on outcomes of children undergoing cranial vault remodeling.[6] Similar to this study, they were unable to perform a hierarchical regression as the PUF does not contain a specific variable to define hospitals. Nevertheless, the results of a hierarchical versus traditional logistic regression model have been compared using NSQIP data, and both types of models yield nearly identical results.[7]

This study has several limitations. The regression analyses in this study are dependent on preoperative variables and do not account for the operative procedure. While this allows for a simpler model, it likely has an effect on the statistical performance of the models. Third, due to the fact that hospital IDs are not available in the PUF, this study could not evaluate the effect of the model in multiple individual hospitals. If interested in studying their risk-adjusted transfusion practices compared to NSQIP-P universe, participating centers can request to the ACS an identification of PUF entries that belong to their institution and perform this analysis. We tested the model in one of the authors' institution PUF entries and the adjustment changed the odds ratio from one side of the null to the other, accentuating the importance of using multivariate models. Finally, the fact that spinal fusion and craniosynostosis surgery accounted for more than half of the transfusions likely leads to increased weighting of variables important to that population of patients (e.g. neuromuscular disorders), which may not be as importantly associated with transfusion in other patient populations.

CONCLUSION

Comparison of perioperative transfusion rates among hospitals should account for patient demographics and risk factors for the event. In the field of pediatrics, young infants and older children have a different surgical profile and a diverse set of risk factors for transfusion. We identified multiple factors to adjust for transfusion rates that are independent of the type of procedure and can be easily and widely used among NSQIP-P participants to benchmark transfusion practices.

CHAPTER 2: Characterizing Perioperative Transfusions in Children's Surgery

SUMMARY

In order to target interventions to optimize the use of perioperative blood products it is relevant to identify surgeries and risk factors associated with transfusions. Data from the National Surgical Quality Improvement Program-Pediatric from 2012 to 2015 were used. CPT (Current Procedural Terminology®) codes were grouped to identify the procedures where the most transfusions are allocated. A total of 369,176 surgical entries were utilized for analysis. Perioperative transfusions occurred in 21,410 (5.8%) of cases. 659 CPT codes were grouped in 207 clusters. Arthrodesis for spinal deformity comprised 44.5% of transfusion occurrences in the dataset and craniectomy for craniosynostosis comprised 8.7%. The majority of RBC transfusions used in children's surgery are concentrated within a relatively few CPT codes. This study assists health centers in focusing blood optimization efforts on common surgeries with high transfusion rates.

INTRODUCTION

In recent years the use of blood products has come under increased scrutiny in an effort to optimize the use of medical resources. Red blood cell (RBC) transfusions have been associated with adverse outcomes including surgical site infection and necrotizing enterocolitis.[8–10] Several randomized trials have shown that restrictive hemoglobin transfusion thresholds are non-inferior to more liberal strategies for both neonates and older pediatric patients,[11–13] and thus a more restrictive approach to transfusion has been recommended. In addition, blood is a non-renewable resource that depends solely on the altruism of donors and thus should not be wasted. For these and other reasons, RBC transfusions have been identified as an important quality metric, and hospitals have put forth significant efforts to decrease their use of blood products.[14,15]

In order to target interventions to optimize the use of blood products related to surgery, the procedures most strongly associated with RBC use must first be identified. Only then can health institutions most efficiently improve their blood transfusions through targeting efforts towards surgeries or patients that are at higher risk of bleeding or anemia. The objective of this study was to characterize the use of transfusions in children's surgery.

METHODS

Data Source

Data from the American College of Surgeons (ACS) National Surgical Quality Improvement Project – Pediatric (NSQIP-P) Participant Use Data Files (PUFs) from 2012 to 2015 were utilized for this analysis. The PUFs contain information on 30-day outcomes on pediatric surgical patients from more than 100 hospitals in the United States, two in Australia, and one in the United Arab Emirates. Pediatric patients were defined as 0 to 18 years of age. A transfusion was defined as an occurrence in which the patient received packed red blood cells, whole blood, or autologous blood transfusion from the surgery start time until 72 hours after. Transfusions received before surgery start time or other blood products (e.g. fresh frozen plasma, platelets, etc.) were not included. The term perioperative transfusion is used for intraoperative and postoperative transfusions, and the perioperative period is defined as a 72 hour window by NSQIP.

Characterization of Transfusion Use

There were a total of 659 CPT (Current Procedural Terminology®) codes in the database. These codes were clustered into 207 groups by similarity of procedures (e.g. one group for codes 22800 to 22812 for arthrodesis of different spinal segments). Transfusion proportions were investigated for individual CPT codes and CPT groups. Cumulative distribution curves were used to visualize the volume of transfusions attributed across the number of CPT codes. Statistical analysis was performed using Stata 15 (College Station, TX).

RESULTS

There were 659 CPT codes listed in the four years of data. There was a transfusion recorded for only 439 of those codes. For CPT codes that occurred at least 10 times, the one with the highest proportion of patients transfused was 21175 (i.e. Reconstruction, bifrontal, superior-lateral orbital rims and lower forehead, advancement or alteration, with or without grafts), with 752 out of 988 (76.1%) cases transfused, although this code only accounted for 3.5% of the total of patients transfused. The codes with the highest contributions to the transfusion counts were 22802 (Arthrodesis, posterior, for spinal deformity, with or without cast; 7 to 12 vertebral segments) and 22804 (Arthrodesis, posterior, for spinal deformity, with or without cast; 13 or more vertebral segments), accounting for 22.8% and 17.6% respectively, of all the transfusions in the dataset. (Table 2.1 & Fig 2.1.A)

Once CPT codes were merged into a shorter list of 207, two groups accounted for more than half of the transfusion in the dataset. The procedures related to arthrodesis for spinal deformity (CPT codes 22280, 22802, 22804 and 22808) comprised 44.5% of the transfusion occurrences in the dataset, and those related to craniectomy for craniosynostosis (CPT codes 61550, 61556, 61557, 61558 and 61559) comprised 8.7%. (Table 2 & Figure 2.1.B)

DISCUSSION

This study used a large national dataset to characterize transfusion use in children's. The majority of transfusions in children's surgery can be attributed to just a few procedures. In fact,

Table 2.1. Procedures with Highest Transfusion Proportions

CPT code(s)	CPT code description	Total	Transfused (%)	% of Total Transfused (n=21,410)
By individual CPT				
21175	Reconstruction, bifrontal, superior-lateral orbital rims and lower forehead, advancement or alteration, with or without grafts	988	752 (76.1)	3.5
22812	Arthrodesis, anterior, for spinal deformity, with or without cast; 8 or more vertebral segments	25	19 (76)	0.1
22804	Arthrodesis, posterior, for spinal deformity, with or without cast; 13 or more vertebral segments	4,972	3,769 (75.8)	17.6
47122	Hepatectomy, resection of liver; trisegmentectomy	48	35 (72.9)	0.2
21180	Reconstruction, entire or majority of forehead and/or supraorbital rims; with autograft	137	99 (72.3)	0.5
By CPT group				
22280, 22802, 22804, 22808, 22810, 22812	Arthrodesis for spinal deformity	14,678	9,532 (64.9)	44.5
61550, 61556, 61557, 61558, 61559	Craniectomy for craniosynostosis	2,986	1,853 (62.1)	8.7
47125, 47130	Hepatectomy, total lobectomy	147	83 (56.5)	3.9
21175, 21779, 21180, 21230	Reconstruction forehead	1,566	883 (56.4)	4.1
51940	Closure, exstrophy of bladder	141	71 (50.4)	0.3

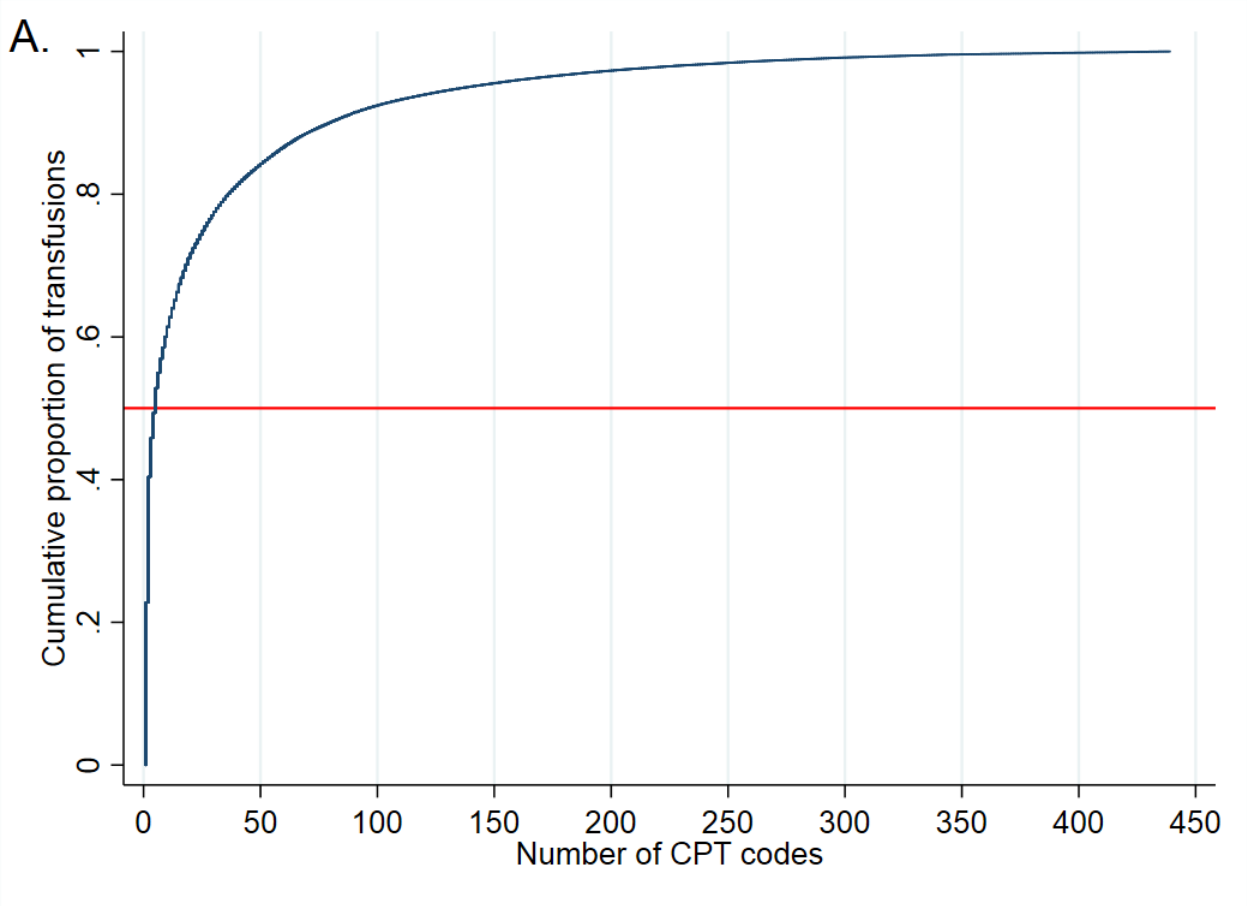

Fig 2.1.A Cummulative proportion of transfusion by individual CPT (Current Procedural Terminology) codes. Each step is one CPT code. The red line is the 0.50 mark. Four CPT codes account for 49.3% of transfusions: 22802 (Arthrodesis, posterior, for spinal deformity, with or without cast; 7 to 12 vertebral segments), 22804 (Arthrodesis, posterior, for spinal deformity, with or without cast; 13 or more vertebral segments, 61559 (Extensive craniectomy for multiple cranial suture craniosynostosis) and 21175 (Reconstruction, bifrontal, superior-lateral orbital rims and lower forehead, advancement or alteration, with or without grafts).

four CPT codes account for half of the intraoperative and postoperative transfusions in children's surgery, and approximately 80% of the transfusions occur within just 10% of the codes. Two categories of procedures—arthrodesis for spinal deformity and craniectomy for craniosynostosis—accounted for over half of the transfusions. This finding suggests that targeting interventions to optimize the use of blood products for these specific surgeries would be most impactful.

To our knowledge, this is the first study outlining the magnitude of transfusion proportions across specific CPT codes in children's surgery. The high rate of blood utilization in pediatric spinal fusions has been studied in surgery-specific analyses. Yoshihara et.al. published trends on transfusion rates for scoliosis surgery extracted from the National Inpatient Sample (NIS) showing transfusion rates of approximately 20-40% depending on the year (2000-2009).[16] That reporting is quite different than the 64.9% identified in this study, presumably because of the

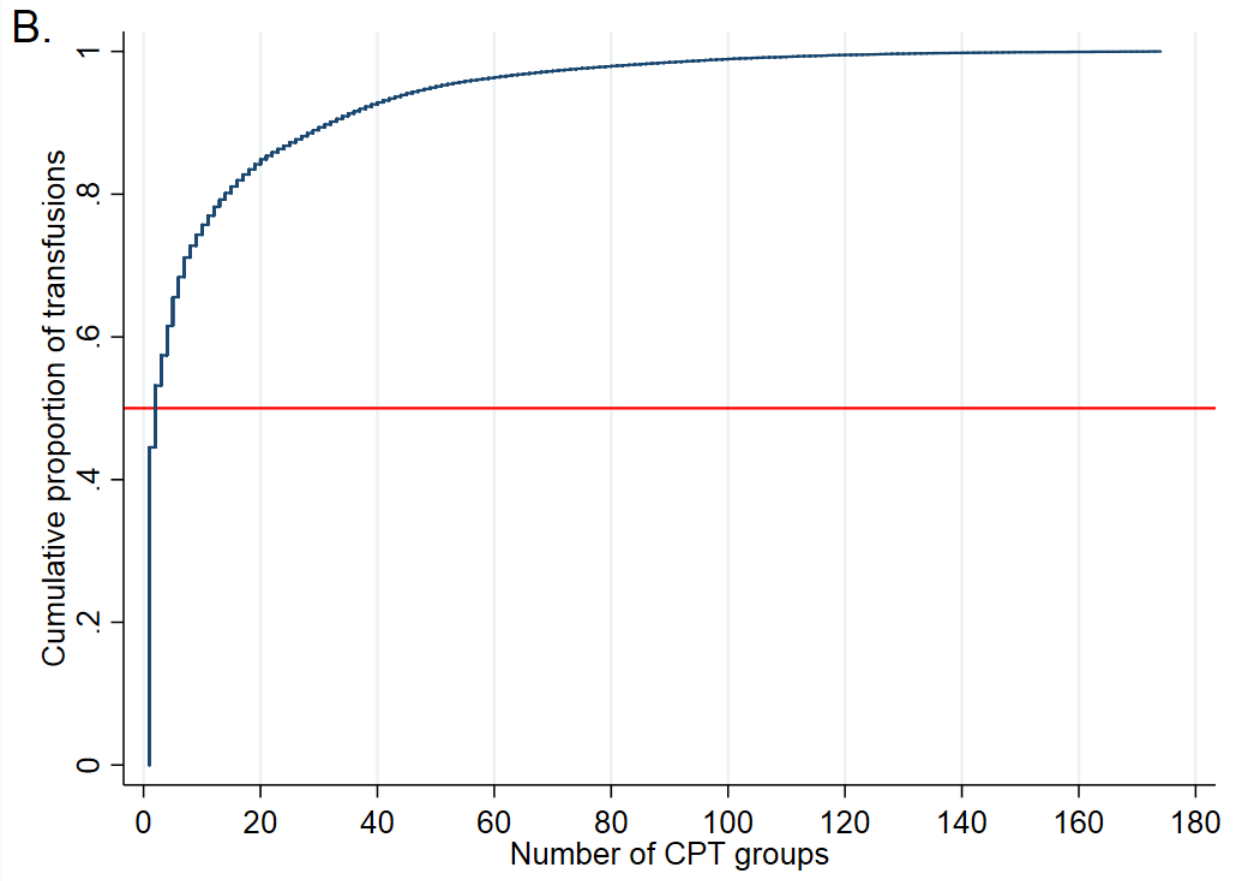

Fig 2.1.B Cummulative proportion of transfusion by CPT (Current Procedure Terminology) groups. Each step is one CPT group. The red line is the 0.50 mark. Two CPT groups account for 53.2% of transfusions: Arthrodesis, posterior and anterior for spinal defomirty, 2 to 13 or more vertebral segments; and craniotomy or craniectomy for craniosynostosis.

coding limitations in capturing all transfusions using NIS. Bowen and colleagues conducted a single-institution analysis that reported a perioperative allogeneic transfusion rate of 57% in this same kind of surgeries.[17] NSQIP-P includes cell salvage methods such as Cell Saver in the definition of transfusion, which may offer an explanation for the small difference between our reported rate and the one from Bowen et.al. Part of the impetus for decreasing blood transfusion is to decrease exposure to allogeneic products. It is important to consider that an unaccounted for, and center-dependent, proportion of transfusions reported in NSQIP-P are from autologous blood.

Similar to scoliosis surgery, transfusion use in craniosynostosis surgery has also been a topic of interest. This study identified that 62.1% of patients undergoing craniosynostosis surgery receive a transfusion, comparable to the rates reported in a systematic review by Lu et.al..[18] Interventions such as the use of preoperative iron supplementation, erythropoietin, autologous pre-donation, intraoperative tranexamic acid, and cell salvage have been suggested for both scoliosis and craniosynostosis operations.[19–21] It is important to mention that a significant limitation of this study is that our data source, NSQIP-P, excludes cardiac and transplant surgery patients, which are populations that certainly encompass a significant volume of transfusions.

CONCLUSION

The majority of RBC transfusions used in children's surgery are concentrated within a relatively few CPT codes. As the appropriate use of blood products becomes more scrutinized, this study

assists health centers in focusing optimization efforts on common surgeries with high transfusion rates such as those for scoliosis or craniosynostosis.

CHAPTER 3: Use of a Clinical Decision Support Tool to Reduce Blood Transfusions in Pediatric Patients.

SUMMARY

A blood transfusion can be a life-saving intervention for a bleeding or anemic patient. However, as most treatments provided in medical care, an overuse of blood transfusion can also lead to an increase in both costs and complications. Using the results from high-quality randomized trials, evidence-based guidelines for transfusion were created as a joint effort from relevant stakeholders at the Johns Hopkins Bloomberg Children's Center (Chapter 4). These guidelines were embedded in a clinical decision support (CDS) logic into our computerized provider ordering system. The effect of this intervention in transfusion rates was analyzed using historical controls in the year immediately prior to the release of the CDS prompt. Several regression models were tested and a zero-inflated negative binomial approach was chosen as the best predictor of the event. The intervention was associated with a significant decrease in transfusion rates in patients >3 months of age (IRR 0.818, $p<0.001$) but not for patients <3 months (IRR 0.972, $p=0.739$). The strength of the evidence supporting our guidelines and the use of hemoglobin thresholds for transfusion is much higher for older children than for neonates. We believe that this was the primary reason for the lack of effect of the CDS intervention. When combining both age groups, the reduction in transfusions per patient-day associated to the use of CDS can be translated to a decrease in 297 transfusions per year.

INTRODUCTION

A blood transfusion can be a life-saving intervention for a bleeding or anemic patient. However, as most treatments provided in medical care, an overuse of blood transfusion can also lead to an increase in both costs and complications. The degree of anemia that a stable child can safely tolerate before receiving benefit from a blood transfusion has recently been investigated for the past 15 years. A randomized trial in critically ill pediatric patients showed that a hemoglobin threshold of 7g/dL was associated with non-inferior outcomes when compared to a more liberal strategy.[12] In extremely low birth weight neonates with anemia of prematurity, restrictive thresholds between 7.5 to 11.5 g/dL depending on age and respiratory support were also deemed non-inferior to higher thresholds when comparing short-term outcomes, although follow up studies have raised concerns for increases in cognitive and neurosensory impairment.[11,22] Further description of the data behind the JHBCC recommendations for transfusion is described in Chapter 4.

Despite this evidence favoring a more conservative approach to blood transfusion in children, transition from clinical trial to clinical application can be slow. Several methods have been shown to improve adherence to evidence based medicine in hospital care.[23] Clinical decision support (CDS) tools have been reported as a way to improve a variety of facets of care, including antibiotic stewardship, timely removal of urinary catheters, appropriate deep venous thrombosis prophylaxis, and prevention of drug interactions.[24–27] The use of CDS for blood utilization in adults has been very promising. Our institution found a decrease in adult RBC utilization of 14.3% when combining CDS with an educational campaign.[28] Evidence for CDS in pediatric

blood utilization, however, is scarce, with only one previous report in a pediatric population and one in neonatal intensive care unit (NICU) patients.[29,30]

The objectives of this study were 1) to implement an evidence-based CDS tool within a computerized provider ordering (CPOE) system and 2) to assess its impact on transfusion practices within a cohort of neonatal and pediatric patients at a large academic children's hospital.

METHODS

Data Source

Patient admissions from a single institution were extracted using IMPACT Online (Haemonetics Corp., Braintree, MA), which is a web-based blood management portal. IMPACT Online contains variables on total use of blood products, length of stay (LOS), hemoglobin level (first, nadir and last), diagnosis and procedure codes, age at admission, and a variety of other factors. The software collects data on transfusion of all blood products, but this analysis focused on allogeneic red blood cell (RBC) transfusions only. A transfusion was defined as a discrete count variable for the delivery of RBC (not specific to a particular ml/kg volume). Monthly reports were created from September 2012 to August 2014. Patients with age at admission from 0 to 18 years were included.

Admissions during which a hemoglobin level was never checked were considered to have no risk of transfusion and were therefore excluded from the analysis. Additional exclusions included

patients who were on extracorporeal life support, had cardiovascular assist devices placed, or underwent transplantation (solid organ or bone marrow) during the hospitalization. Finally admissions with a Diagnosis Related Group code of an injury or trauma (codes 901 to 923 and 955 to 965) and a length of stay (LOS) ≤1 day were excluded as those transfusions were likely related to massive transfusion protocols and therefore unlikely to be impacted by any CDS intervention. Only admissions that began and ended within the study period were analyzed. If a patient was admitted before the intervention but discharged after that entry was removed from the dataset to avoid partial exposure to the CDS intervention.

A subset of surgical patients was created using a definition described previously.[31] In brief, surgical admissions were defined as those admissions that included a surgical ICD9 code as the primary procedure for the admission. ICD9 codes 35.00 to 35.99 were also included to account for cardiac surgery patients. Even though this definition does not include all patients that underwent an operation during their admission, it encompasses a representative sample of primary surgical patients.

Intervention

The intervention of interest was a CDS tool embedded within the CPOE system. At the time that blood transfusion was ordered, the last hemoglobin value on the patient record was automatically extracted. A message appeared if the transfusion was not compliant with the hemoglobin thresholds defined in institutional recommendations for blood use. These recommendations were developed by an institutional working group based upon the best evidence available at that time (Table3.1) The message was a "soft" stop that displayed a text reminding the provider of the

evidence suggesting that the transfusion may not be necessary and then required the user to choose an indication from a list of options before continuing with the order. This message was not a "hard" stop preventing the order entirely, but rather the prompt required an extra step to justify the transfusion in order to proceed with the order if it was still desired.

The study population was stratified by age at admission: patients zero to 3 months (90 days) of age and those >3 months to 18 years. The CPOE prompt was activated by different thresholds depending on the age group. For patients 0 to 3 months or in the NICU, the pre-transfusion trigger was ≥8.5 g/dL and for older patients it was ≥7g/dL. The institutional recommendations allowed for three different hemoglobin thresholds for patients 0 to 3 months of age depending on age and need for respiratory support. Since the software algorithm did not allow for this level of detail, the CDS prompt for patients <3 months of age included the table of recommendations and an option to click on "transfusion is compliant with guidelines" in the list of indications. (Table 3.1)

The CDS tool was the main intervention of a group of efforts to optimize the use of blood products at our institution. Other associated components were dissemination of recommendations via wallet-size cards, presentations at grand rounds and educational conferences, and discussions at divisional meetings. In order to minimize the magnitude of the effect of the CDS tool, all of these occurred prior to the release of the prompt and at different time points during the preceding year.

Table 3.1 Institutional recommendations for hemoglobin thresholds for transfusion and exceptional indications

Patients 0 to 3 months of age or in the NICU

Age, days	Respiratory Support*	No respiratory support
1 to 7	≤13.5 g/dL	12.0 g/dL
8 to 14	≤12.0 g/dL	≤10.0 g/dL
≥ 15	≤10.0 g/dL	≤8.5 g/dL

Indications to transfuse over hemoglobin recommendation:
Active bleeding
Hemolysis
Active cardiac disease
Active pulmonary disease
Symptoms attributed to anemia
Other

Patients > 3 months of age

< 7 g/dL for all

Indications to transfuse over hemoglobin recommendation:
Active bleeding
Active cardiac disease
Active pulmonary disease
Acute coronoary or cerebral ischemia
Primary oncologic disease
Sickle cell disease
Other primary hematologic disease
Other

NICU, neonatal intensive care unit.
* respiratory support is defined as any use of oxygen supplementation

The data for a two year period were analyzed: the immediate calendar year prior to the CDS intervention was used as a control cohort and compared to the year after the intervention was implemented (day 0 being the first day that the CDS tool appeared in the CPOE).

Outcomes & Statistical Analysis

The primary outcome of interest was the difference in the number of transfusions per patient-day. This was obtained by calculating incidence rates of allogeneic RBC transfusion events during the hospital stay of every patient. Secondary outcomes included mean nadir and last hemoglobin values for the hospital stay, number of transfusions per patient, LOS, number of patients transfused, number of frequently transfused patients (defined as ≥10 transfusions) and the number of transfusions given to frequently transfused patients. Demographic variables (age and sex), case mix index (CMI, a continuous variable based on the Medicare Severity-Diagnosis Related Group weights), and the mean first hemoglobin were analyzed to verify that the populations before and after the CDS intervention had similar profiles. The chi-square test was used to compare categorical variables, the t test was used to compare means of variables with a normal distribution, and a K-sample equality-of-medians test was used for non-parametric comparisons.

Transfusion use before and after the CDS intervention was compared using several methods: 1) crude incidence rate ratios (IRR), 2) negative binomial (NB) regression models, and 3) zero-inflated negative binomial (ZINB) regression models. Model performance was compared using the Akaike information criterion (AIC).[32] The model with the lowest AIC was considered the best performing. Multivariate models were adjusted for age in years (only for the age group >3 months), sex, type of patient (primarily surgical versus not), and CMI. Zero inflated (ZI) regression models were utilized due to the high number of patients that were not transfused during their hospital stay, and these were inflated with age in years and nadir hemoglobin..

Poisson regression was not utilized since the median and variance of the sample were significantly different.

A subset analysis was done to investigate outcomes specifically within surgical patients, and a sensitivity analysis was performed excluding patients that were frequently transfused during their hospital stay. Statistical analysis was performed using STATA/MP 15.1 (College Station, TX).

RESULTS

A total of 23,756 admissions were screened. After applying exclusion criteria, 14,075 pediatric admissions were included in the two year analysis, 3,296 in the 0-3 month age group and 10,779 in the 3 months to 18 years group. (Figure 3.1)

Admissions 0 to 3 months of age

No significant differences were identified in the characteristics of patients before (n=1,612) and after (n=1,684) the intervention. Median age at admission was 0 [0-2] before the intervention and o [0-0] after, 42.9% of patients were female before the prompt and 44.3% after (p=0.723). The mean CMI (MSDRG weights) was 2.12 ±1.44 and 2.09 ±1.45 (p=0.637). The mean first hemoglobin was 16.0 ±3.3 and 16.1 ±3.2 for the two time periods (p=0.221). (Table 3.2)
The incidence of transfusions per patient-day was 0.060 before the intervention and 0.053 after (IRR 0.883, p=0.007). (Figure 3.2) The mean nadir (14.6±3.6 vs. 14.8±3.5, p=0.155) and last (15.3±3.2 vs. 15.4±3.2, p=0.374) hemoglobin levels were not different in the control and

intervention cohorts. A total of 223 (13.8%) patients were transfused in the year before the intervention and 219 (13.1%) in the year after (p=0.485). Thirty children were frequently transfused (≥10 times) and received 49.9% of the transfusions in the control group, and 18 patients were frequently transfused and received 35.3% of the transfusions in the intervention group (p<0.001). The median LOS was not different between the cohorts (3 days [2-9] vs. 4 days [2-9], p=0.413). (Table 3.3)

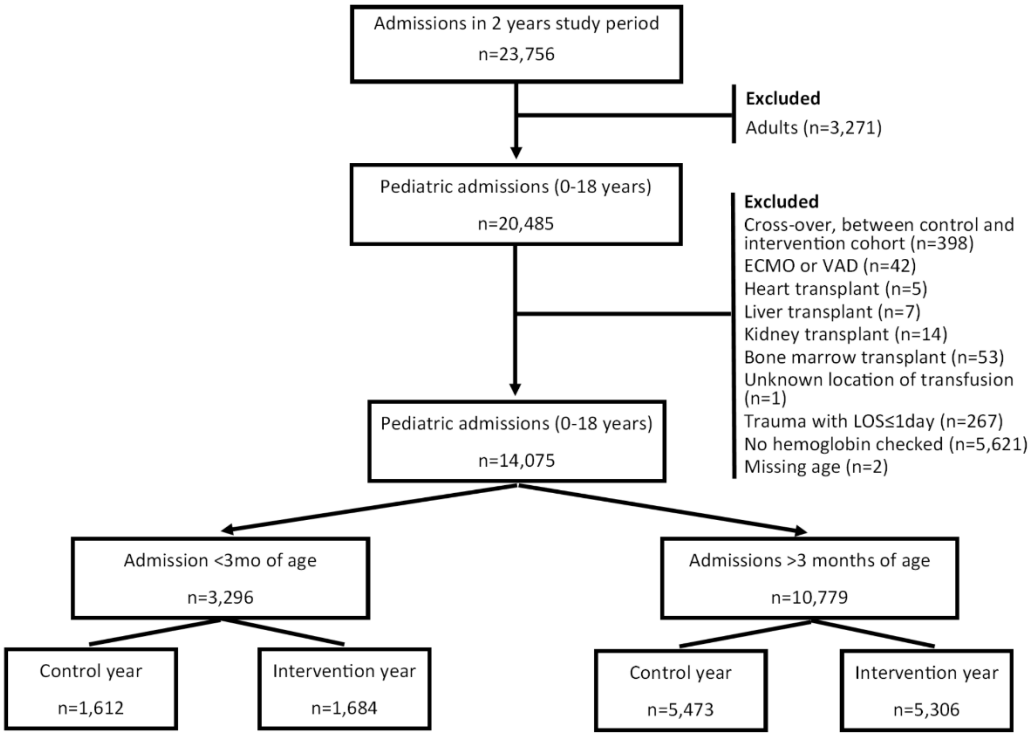

Fig 3.1 Patient flow chart and exclusion criteria. ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; LOS, length of stay

The incidence of transfusions in surgical patients (n=355) was 0.070 before the intervention and 0.066 after (IRR 0.951, p=0.542). Secondary outcomes were again similar in the time period before and after the intervention. The mean nadir (11.5±2.9 vs. 11.5±3.0, p=0.986) and last (13.0±2.7 vs. 12.8±2.9, p=0.653) hemoglobin levels were similar, as well as the number of patients transfused (45.1% vs. 41.3%, p=0.469) and LOS (15 days [5-38] vs. 14 days [5-27], p=0.548). (Table 3.4)

When excluding the frequently transfused patients, the difference in transfusion incidence before and after the intervention was no longer seen. The incidence of transfusions was 0.037 before the intervention and 0.039 after (IRR 1.061, p=0.339). The secondary outcomes were also similar: nadir mean hemoglobin was 14.7±3.5 vs. 14.9±3.5 (p=0.268) and last hemoglobin was 15.4±3.2 vs. 15.4±3.2 (p=0.529). (Table 3.5)

Table 3.2 Population Characteristics by Age Group & CDS intervention

	< 3 months			**3 months to 18 years**		
	Pre-CDS n=1,612	Post-CDS n=1,684	*p*	Pre-CDS n=5,473	Post-CDS n=5,306	*p*
Age,median [IQR]	0 days [0-2]	0 days [0-0]	n/a	8 years [3-14]	9 years [3-14]	0.030
Age category,n (%)						
0 to 3 months	-	-		-	-	
3 months to 1y	-	-		591 (10.8)	491 (9.3)	
1 to 10 years	-	-		2,402 (43.9)	2,319 (43.7)	
11 to 18 years	-	-		2,480 (45.3)	2,496 (47.0)	0.017
Sex, female n(%)	724 (42.9)	746 (44.3)	0.723	2,617 (47.8)	2,579 (48.6)	0.413
CMI, mean ±SD	2.12 ±1.44	2.09 ±1.45	0.637	1.63 ±1.52	1.66 ±1.54	0.394
First Hb, mean g/dL ±SD	16.0 ± 3.3	16.1 ±3.2	0.221	11.9 ±2.1	11.7 ±2.1	<0.001

CDS, clinical decision support; CMI, case-mix index; Hb, hemoglobin

Admissions >3 months to 18 years

Characteristics of patients before (n=5,473) and after (n=5,306) the intervention were generally similar. The median age at admission was slightly younger during the control period (8 years [3-14] vs 9 years [3-14], p=0.030), likely related to a higher proportion of patients in the 11-18 year age group in the intervention group (45.3% vs. 47.0%). In addition, the mean first hemoglobin value was slightly higher in the time period before the intervention (11.9±2.1 vs 11.7±2.1, p<0.001). (Table 3.2)

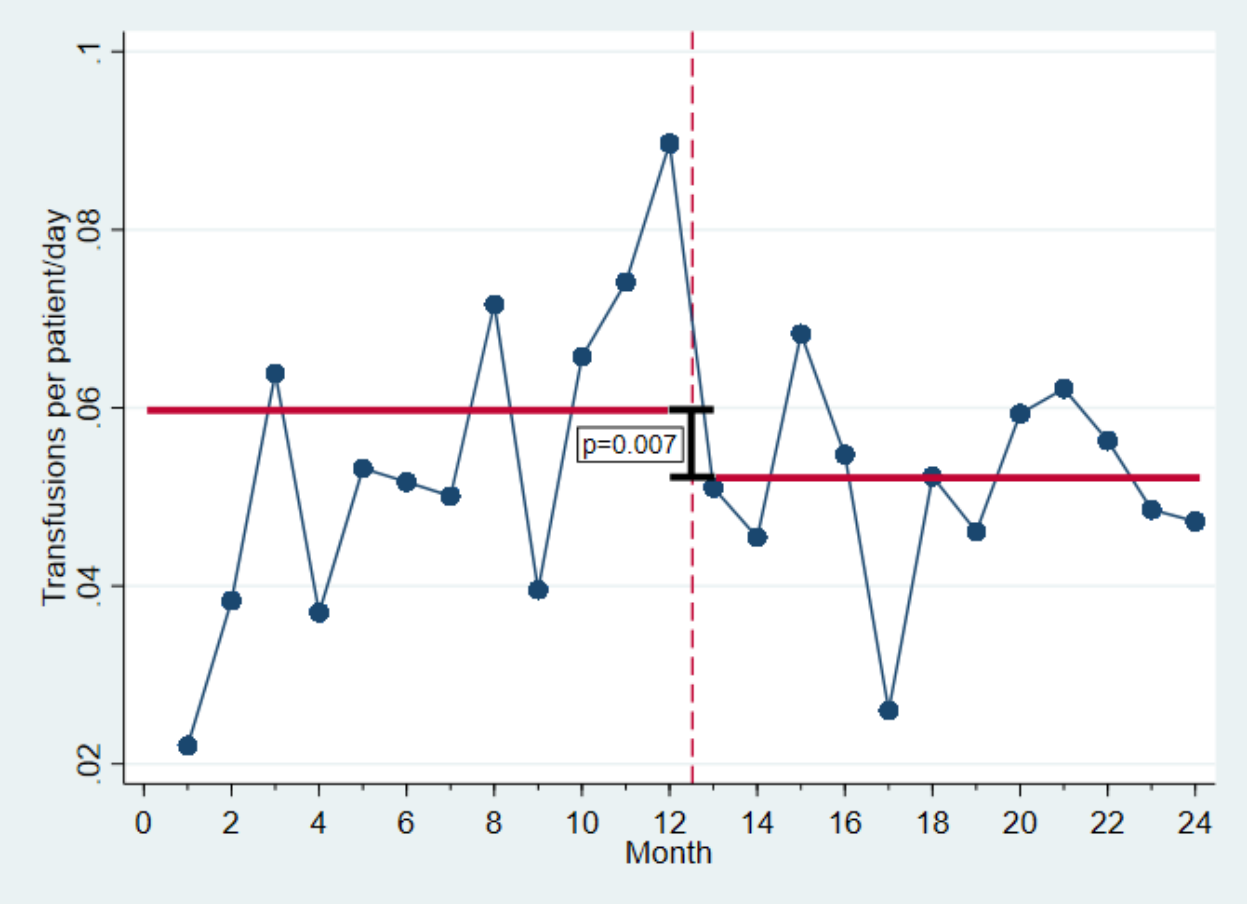

Fig 3.2 Monthly rates of transfusions per patient/day for patients <3 months of age or in the neonatal intensive care unit. Solid red line is the incidence rate for the 12-month period. Dashed red line is the time of the clinical decision support intervention launch. The crude incidence rate ratio (IRR) was 0.883 (p=0.007). The IRR on the multivariate zero-inflated negative binomial regression model was 0.972 (p=0.739).

The incidence of transfusions per patient-day was 0.067 before the intervention and 0.061 after (IRR 0.906, p=0.003). (Figure 3.3) The mean nadir hemoglobin (10.8±2.4 vs. 10.6±2.5, p=0.001) and last hemoglobin (11.5±2.0 vs. 11.3±2.0, p<0.001) were slightly lower in the time period after the intervention. A total of 726 (13.3%) patients were transfused in the year before the intervention and 661 (12.5%) in the year after (p=0.211). Twenty children were frequently transfused (≥10 times) and received 13.8% of the transfusions in the control group, and 21 patients were frequently transfused and received 18.0% of the transfusions in the intervention group (p=0.001). The median LOS was not different between the two cohorts (3 days [2-6] vs. 3 days [2-6], p=0.378). (Table 3.3)

Table 3.3 Secondary Outcomes by Age Group & CDS intervention

	< 3 months			**3 months to 18 years**		
	Pre-CDS n=1,612	Post-CDS n=1,684	*p*	Pre-CDS n=5,473	Post-CDS n=5,306	*p*
Nadir Hb, mean g/dL ±SD	14.6 ±3.6	14.8 ±3.5	0.155	10.8 ±2.4	10.6 ±2.5	0.001
Last Hb, mean g/dL ±SD	15.3 ±3.2	15.4 ±3.2	0.374	11.5 ±2.0	11.3 ±2.0	<0.001
n of patients transfused, n(%)	223 (13.8)	219 (13.1)	0.485	726 (13.3)	661 (12.5)	0.211
n of transfusions per patient, n(%)						
0	1,389 (86.2)	1,465 (87.0)		4,747 (86.7)	4,645 (87.5)	
1	76 (4.7)	81 (4.8)		278 (5.1)	275 (5.2)	
2	42 (2.6)	40 (2.4)		207 (3.8)	171 (3.2)	
3	21 (1.3)	21 (1.3)		81 (1.5)	68 (1.3)	
4	21 (1.3)	16 (1.0)		58 (1.1)	58 (1.1)	
5-9	33 (2.1)	43 (2.6)		82 (1.5)	68 (1.3)	
≥10	30 (1.9)	18 (1.1)	0.058	20 (0.4)	21 (0.4)	0.798
n of transfusions to patients transfused ≥10 times, n(%)	509 (49.9)	306 (35.3)	<0.001	272 (13.8)	322 (18.0)	0.001
Length of stay, median [IQR]	3 [2-9]	4 [2-9]	0.413	3 [2-6]	3 [2-6]	0.378

CDS, clinical decision support; Hb, hemoglobin.

The incidence of transfusions in surgical patients (n=2,220) was 0.107 before the intervention and 0.103 after (IRR 0.960, p=0.424). Mean nadir hemoglobin was no different before and after the intervention (10.5±2.2 vs. 10.4±2.2, p=0.245), but the mean last hemoglobin was slightly lower in the time period after the intervention (11.2±1.9 vs. 11.0±1.9, p=0.014). The number of patients transfused (23.9% vs. 22.0%, p=0.288) and LOS (4 days [2-7] vs. 4 days [2-7], p=0.602) were not different. (Table 3.4)

Table 3.4 Secondary Outcomes by Age Group & CDS intervention for Surgical Patients.

	< 3 months			**3 months to 18 years**		
	Pre-CDS n=184	Post-CDS n=179	*p*	Pre-CDS n=1,149	Post-CDS n=1,071	*p*
Nadir Hb, mean g/dL ±SD	11.5 ±2.9	11.5 ±3.0	0.986	10.5 ±2.2	10.4 ±2.2	0.245
Last Hb, mean g/dL ±SD	13.0 ±2.7	12.8 ±2.9	0.653	11.2 ±1.9	11.0 ±1.9	0.014
n of patients transfused, n(%)	83 (45.1)	74 (41.3)	0.469	275 (23.9)	236 (22.0)	0.288
n of transfusions per patient, n(%)						
0	101 (54.9)	105 (58.7)		874 (76.1)	835 (78.0)	
1	23 (12.5)	25 (14.0)		89 (7.8)	77 (7.2)	
2	16 (8.7)	16 (8.9)		71 (6.2)	56 (5.2)	
3	11 (6.0)	10 (5.6)		41 (3.6)	30 (2.8)	
4	10 (5.4)	6 (3.4)		29 (2.5)	25 (2.3)	
5-9	15 (8.2)	14 (7.8)		38 (3.3)	40 (3.7)	
≥10	8 (4.4)	3 (1.7)	0.751	7 (0.6)	8 (0.8)	0.820
Length of stay, median [IQR]	15 [5-38]	14 [5-27]	0.548	4 [2-7]	4 [2-7]	0.602

CDS, clinical decision support; Hb, hemoglobin.

When excluding the frequently transfused patients, the difference in transfusion incidence before and after the intervention persisted. The incidence of transfusions per patient-day was 0.059

before the intervention and 0.052 after (IRR 0.876, p<0.001). The differences in secondary outcomes also remained: the mean nadir hemoglobin was 10.8±2.4 vs. 10.7±2.4 (p=0.001) and last hemoglobin was 11.5±2.0 vs. 11.3±2.0 (p<0.001). (Table 3.5)

When combining both age groups, the incidence of transfusions per patient-day was 0.065 before the intervention and 0.058 after (a decrease of 10%). This reduction can be extrapolated to a decrease of 297 transfusions/year associated with the intervention in this size study population.

Table 3.5 Outcomes by Age Group & CDS intervention excluding patients transfused ≥10 times

	< 3 months			**3 months to 18 years**		
	Pre-CDS n=1,582	Post-CDS n=1,666	*p*	Pre-CDS n=5,453	Post-CDS n=5,285	*p*
Nadir Hb, mean g/dL ±SD	14.7 ±3.5	14.9 ±3.5	0.268	10.8 ±2.4	10.7 ±2.4	0.001
Last Hb, mean g/dL ±SD	15.4 ±3.2	15.4 ±3.2	0.529	11.5 ±2.0	11.3 ±2.0	<0.001
n of patients transfused, n(%)	193 (12.2)	201 (12.1)	0.906	706 (13.0)	640 (12.1)	0.190
Length of stay, median [IQR]	3 [2-8]	4 [2-9]	0.259	3 [2-6]	3 [2-6]	0.407

CDS, clinical decision support; Hb, hemoglobin.

Regression Modeling

In addition to the crude IRR, four regression models were tested for each age group: a univariate NB model, a multivariate NB model, a univariate ZINB, and a multivariate ZINB . (Table 3.6)The test for alpha on all the NB models was statistically significant, confirming that the data is better fit by the NB distribution compared to the Poisson. In addition, the AIC was better for

the ZI models, suggesting an improved predictability when weighting the highly frequent zero counts. For patients <3 months of age, the IRR shifted towards the null as the regression model performed better (reduced AIC), with the best performing option being the ZINB model. The IRR for the multivariate ZINB model in the <3 month group was 0.972 (95%CI 0.821-1.150), negating the difference seen in the crude IRR within this age category. The models for the cohort of patients >3 months had the opposite effect, with the IRR shifting away from the null as the model performed better. The IRR for the multivariate ZINB model was 0.818 (95%CI 0.732-0.914), confirming the significant decrease in the incidence of transfusion after the intervention within the > 3 months of age group of children.

Table 3.6. IRR for the CDS prompt in different regression models

	IRR	95%CI	p	SE	z	AIC
< 3 months						
crude IRR	0.883	0.806-0.968	0.007			
univariate NB *	0.914	0.767-1.088	0.312	0.081	-1.01	3615
multivariate NB **	0.964	0.803-1.156	0.692	0.090	-0.40	3368
univariate zero-inflated NB ***	0.980	0.832-1.153	0.805	0.082	-0.25	2756
multivariate zero-inflated NB	0.972	0.821-1.150	0.739	0.838	-0.33	2653
3 months to 18 years						
crude IRR	0.906	0.850-0.966	0.003			
univariate NB*	0.824	0.728-0.934	0.002	0.053	-3.03	12100
multivariate NB**	0.833	0.734-0.946	0.005	0.054	-2.83	11609
univariate zero-inflated NB***	0.809	0.722-0.906	<0.001	0.047	-3.69	9934
multivariate zero-inflated NB	0.818	0.732-0.914	<0.001	0.046	-3.55	9542

IRR, incidence rate ratio; CDS, clinical decision support; SE, standard error; AIC, Akaike information criterion; NB, negative binomial.

* negative binomial models using length of stay as exposure.

** multivariate models adjusted for sex, age (in years), surgical patient and case-mix index

*** zero-inflated models were inflated for age (in years) and nadir Hb

DISCUSSION

This study evaluated the implementation of an evidence-based CDS tool within a large children's hospital CPOE system as an intervention to reduce transfusions during neonatal and pediatric hospitalizations. After introducing the CDS tool, a significant decrease in the incidence of transfusion was noted amongst children >3 months of age. Specifically, when compared to the time period before the intervention, the incidence of transfusion in children >3 months of age decreased by 18% (IRR 0.818, $p<0.001$). Interestingly, however, the incidence of transfusion did not significantly change for children <3 months of age (IRR 0.972, $p=0.739$).

The use of CDS in blood utilization has been reported previously within the pediatric population. Out of the four published pediatric studies, one specifically examined platelet and plasma transfusion,[33] and another was focused on exchange transfusions in patients with sickle cell disease.[34] Of the two studies that examined RBC transfusions, one was NICU specific while the other excluded NICU patients. Baer and colleagues introduced their institutional guidelines into a CDS algorithm for NICU patients. Their intervention was associated with a decrease in transfused patients from 19 to 13 percent ($p<0.05$).[30] In 2011, Adams et.al. showed a significant decrease in the rate of transfusion with a prompt that reminded clinicians of the evidence that a hemoglobin threshold of 7g/dL is safe.[29] In this study, patients in the NICU as well as those on cardiac and hematology/oncology wards were excluded. The study showed a decrease in transfusions per patient day from 0.076 to 0.050 ($p<0.03$). We modeled our intervention in a similar way to this study but included a separate algorithm for patients in the NICU. In addition, due to the fact that our cardiac and hematology/oncology patients are not completely

geographically separate from the rest of the pediatric intensive care unit and general ward we chose to include them in our analysis. We did, however, exclude transplant patients and those on extracorporeal support due to the lack of evidence for hemoglobin thresholds in these populations.[35,36]

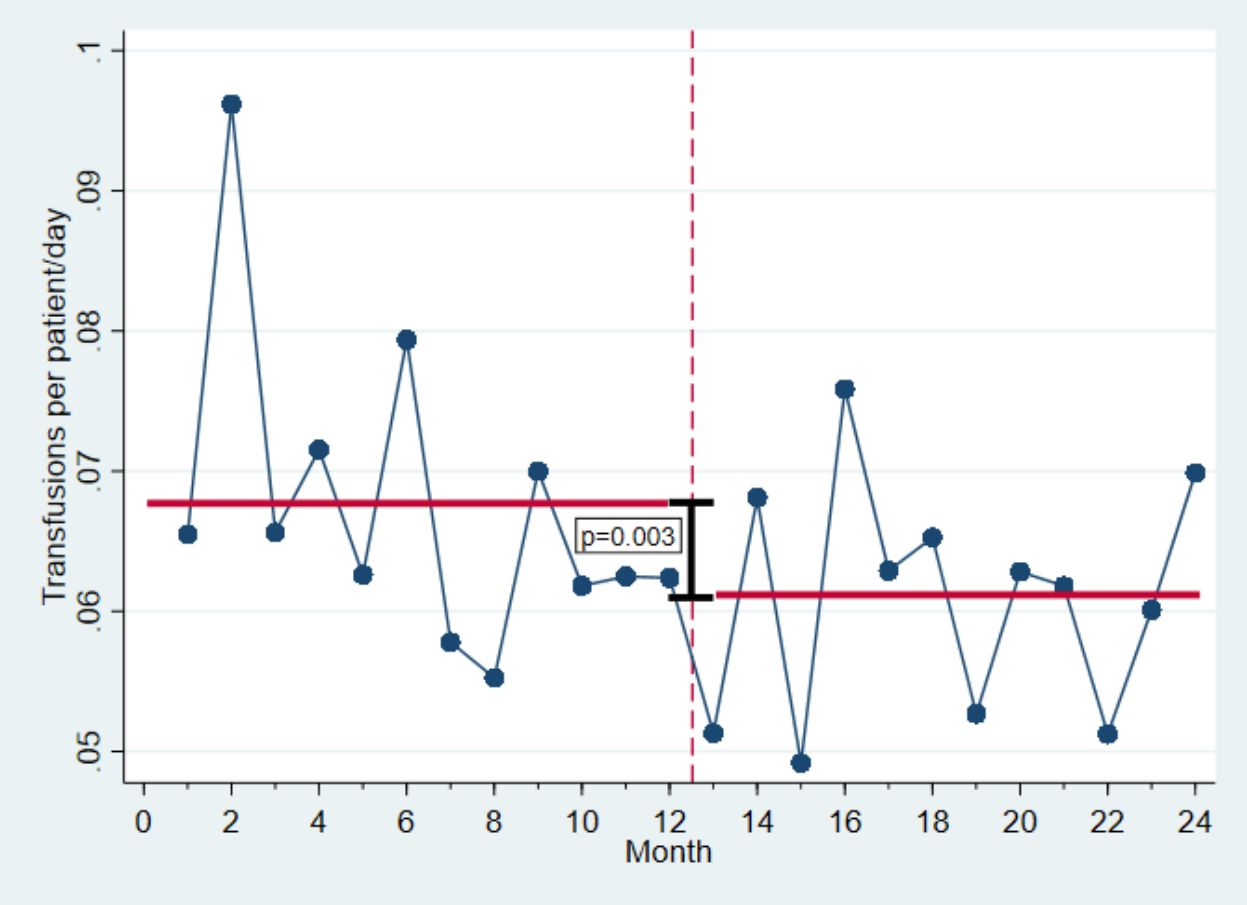

Fig 3.3 Monthly rates of transfusions per patient/day for patients >3 months of age. Solid red line is the incidence rate for the 12-month period. Dashed red line is the time of the clinical decision support intervention launch. The crude incidence rate ratio (IRR) was 0.906 (p=0.003). The IRR on the multivariate zero-inflated negative binomial regression model was 0.818 (p<0.001).

A systematic review by Hibbs et.al. examining the use of CDS tools with regard to transfusion practices found only modest success. The study, which also included adult patients, found that of

the 13 studies included only 7 showed a statistically significant reduction in transfusions, of which two studies were mentioned previously above.[37] Outcomes such as LOS and mortality were unchanged in most studies. The economic argument is a compelling one when analyzing the benefit of a health intervention and all of the studies in the systematic review by Hibbs et.al. were associated with a decrease in costs.[37] The data behind monetary costs of a pediatric transfusion are limited. Since the actual financial burden of a blood transfusion is dependent on many factors such as volume, location of patient, characteristics of the RBC (e.g. leukoreduced, same donor, etc) we cannot safely extrapolate costs reported in publications of transfusions in adults to transfusions in children therefore cannot calculate an accurate amount on the economic effects of our intervention.[38]

To investigate the effect of CDS tools on transfusions practices, multiple potential outcomes could be studied. The most commonly used metrics are monthly or aggregate rates of transfusion, mean pretransfusion hemoglobin, adherence to specific transfusion guidelines, number of transfusions per patient, and proportion of patients transfused. The mean pretransfusion hemoglobin offers an easy to compare continuous and likely normally distributed variable that can also report adherence to guidelines, but it is also resource intensive to collect. We used IMPACT Online as our primary data source, which automatically calculates counts of blood transfusions as well as first, nadir, and last hemoglobin. We chose to use transfusion rate as our outcome instead of pretransfusion hemoglobin due to the ease with which tranfusion rate can be ascertained and immediately translated to resource utilization. One of the limitations of the retrospective review of rates that we and other authors have encountered is that it can be greatly dependent on small changes in population characteristics and severity of disease within

the cohorts. We attempted to account for this limitation by creating regression models that adjust for age, sex, and severity of disease.

One of the challenges that comes with analyzing counts in transfusion data is that most hospitalized patients do not require a transfusion. The excessive amount of zeros can compromise the interpretation of the comparison by ignoring the effect of not transfusing an anemic patient. By introducing a ZI model, a different approach is applied to a patient that was not transfused but had a low nadir hemoglobin compared to one that was never anemic and therefore had a negligible risk of getting transfused. ZI models include a binary (logit or probit) model with a count model (Poisson or NB) and have the same ability to introduce covariates as most regression models.[39] While most studies of CDS effectiveness have used crude incidence rates, we believe that a ZI count model such as ZINB, hurdle, or Poisson (if the assumptions of its distribution hold) are more appropriate.[40,41] In addition, we have shown that use of a ZI model may significantly alter inferences—in this study no difference in transfusion rates was found in infants <3 months when appropriately analyzed with a ZI model despite the crude IRR initially suggesting a difference.

Randomized trial data supports the use of conservative hemoglobin thresholds for transfusion in pediatric patients, but the validation and widespread acceptance of the data has been slower in the neonatal population. Kirpalani et.al. conducted a randomized trial in extremely low birth weights comparing low and high hemoglobin triggers for transfusion.[11] The study demonstrated no differences in complications between the two groups. However, there has been continued hesitancy to use restrictive hemoglobin thresholds in neonates, primarily due to the concern for

effects of anemia on the developing brain.[42] Three years after the Kirpalani et.al. trial, a follow up study of the same patients showed a trend towards higher cognitive delay (24.4% in the low threshold group vs. 17.6% in the high, p=0.06) in the restrictive threshold group.[22] This likely led to significant caution amongst neonatologists with regard to the their approach to anemia. Indeed an international survey showed widely varying approaches to hemoglobin thresholds among neonatologist, with a range of discrepancy around 2g/dL for most physicians.[43] We suspect this concern for cognitive development and variability in beliefs about transfusion thresholds in the neonatal population amongst is why the CPS tool in this study failed to show a difference in transfusion rates in the <3 month age group.

The data to support restrictive thresholds in older children is more widely accepted compared to neonates. The main trial supporting a hemoglobin of 7g/dL as a transfusion threshold was published in 2007 by Lacroix et.al. and showed no difference in morbidity when comparing it to a liberal threshold of 9.5g/dL.[12] They excluded patients that were hemodynamically unstable or had acute blood loss, hemolytic anemia, or cardiovascular problems. Post-hoc subgroup analyses were done in septic, cardiac, and general surgical patients with concordant results showing no increase in adverse effects with restrictive thresholds.[13,44,45] These and other studies were consolidated in 2018 into a group of recommendations from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative that states “In critically ill children or those at risk for critical illness, who are hemodynamically stable and who have an hemoglobin concentration greater than or equal to 7g/dL, we recommend not administering a RBC transfusion.”.[46] Despite this, the mean nadir hemoglobin of the patients >3 months of age in our cohorts was 10.6 g/dL to 10.8 g/dL, questioning whether we had a significant volume of patients that fell out of the

generalizable population for the recommendations (e.g. unstable, cardiovascular problems) or whether institutional adherence to guidelines was simply that low. The institutional adherence to guidelines was examined in a Chapter 4.

It is important to recognize the details of our inclusion and exclusion criteria and how that applies to a generalization of our findings. A significant proportion of blood products utilized in a hospital goes to a small number of patients. Most patients at high risk of frequent transfusions are trauma patients, critically ill patients on extracorporeal life support, critically ill premature infants, patients with hemorrhagic shock, bone marrow suppression, or an inherited blood disorder, or patients undergoing surgeries that are associated with high blood loss (e.g. cardiac surgery, spinal surgery).[47] The CPOE intervention in this study was applied to every transfusion order that occurred in the wards (intensive care unit and general floor) but excluded transfusions in the operating room, in outpatient areas, and those associated with massive transfusion protocols. Patients that were transplanted (solid organ or bone marrow), had a trauma with a LOS ≤1 day, or who had been on extracorporeal life support or had a cardiovascular assist device placed were excluded. The rationale for this exclusion was the lack of evidence to support hemoglobin threshold in these particular populations and because trauma patients with a short LOS were either minimally injured and therefore discharged and not at risk of transfusion or so severely injured that they died, frequently from hemorrhagic shock and therefore making their blood requirements likely the result of activating a massive transfusion protocol. In addition, admissions that never had a hemoglobin checked were excluded, leading to an inflation of our transfusion per patient-day rate. These exclusions make comparison of transfusion rates between

hospitals unreliable but if maintained constant with a given institution may still allow for longitudinal analyses within that hospital.

Several limitations of this study should be noted. From the methodological perspective, historical controls were used for comparison, and these data were obtained retrospectively, adding risk for potential bias. The data was analyzed with the assumption that the control and intervention cohorts were similar and had the same risk of receiving blood. Even though the regression models were adjusted for age, gender, and CMI, there is still potential for residual confounding. In addition, the exclusion criteria applied to the cohorts removed patients that potentially had high transfusion rates, which could skew the IRR significantly. Finally, this study focused on the impact of a CDS tool on transfusion rates, but the power of the intervention is certainly affected by the perceived strength of the data on which the CDS prompt is based. Clinicians consider many data points when making a decision to transfuse, and an improved intervention with physiologic parameters (e.g. blood pressure, heart rate, oxygen requirements, and measures of tissue perfusion) may have an even stronger impact on transfusion practices.

CONCLUSION

CDS is a useful tool to disseminate institutional guidelines and evidence-based practices. CDS providing guidance on hemoglobin thresholds for transfusion and embedded within a CPOE system decreased transfusion rates in pediatric patients but not amongst the youngest neonates, a population in whom the evidence for transfusion thresholds is less robust. Comparisons of

transfusion practices over time should utilize a statistical model that appropriately accounts for the high proportion of zero events, as inferences may be altered with this approach.

CHAPTER 4: Institutional adherence to Hb based guidelines for transfusion

SUMMARY

In this chapter, we report our adherence to the guidelines described in chapter 3 as well as the indications that patients have when receiving transfusions outside of recommended thresholds. Transfusions from August 28, 2013 to October 31, 2014 at the JHBCC were analyzed. The primary outcome was the proportion of transfusions compliant with hemoglobin-level based recommendations. This was studied for both age groups and for each hospital location (NICU, PICU and regular inpatient floor). Our final cohort consisted of 1,955 pediatric transfusions of which 1,104 occurred in patients <3 months of age or in the NICU and 851 in patients >3 months of age. The proportion of compliant transfusion orders in patients <3 months of age varied by hospital location with 386 (42.6%) compliant transfusions in the NICU, 116 (63.4%) in the PICU and 13 (92.9%) in the floor ward ($p<0.001$). The same variation occurred in children >3 months, with 158 (27.8%) compliant transfusions in the PICU and 141 (50.0%) in the acute care floor ($p<0.001$). The most common indications stated by providers were active cardiac disease, active bleeding and symptomatic anemia. As hospitals implement guidelines for transfusion practices it is relevant to constantly evaluate institutional adherence and identify populations where unnecessary transfusions may be decreased.

INTRODUCTION

There are multiple variables that are considered when deciding to give a blood transfusion. It is relevant to recognize the child's physiology, age, oxygen delivery, bone marrow activity, acute blood loss, surgical plan, among other factors. One of the most universal markers that clinicians take into account is the hemoglobin (Hb) level. Even though Hb is a single variable in the equation, it offers an easy to measure, trackable and dynamic variable that can indicate the need of a blood transfusion. The most relevant studies in anemia tolerance of hospitalized patients have used Hb level as the trigger to transfuse

Randomized trials to study restrictive hemoglobin thresholds have been done in pediatrics for more than a decade. Bell et.al. first published a study 2005 in 100 preterm infants with weight of 500 to 1300g. Their restrictive threshold was defined depending on the patients respiratory level of support, ranging from a hematocrit from 22 to 34 (Hb approximately 7.3 to 11.3 g/dL) and the liberal from 30 to 46 (Hb approximately 10 to 15.3 g/dL). As expected, the infants in the restrictive threshold received less transfusions but also had an increase in grade 4 intraventricular hemorrhage (0% vs. 8 %, p=0.012) and apneic episodes per day requiring stimulation (0.23 vs. 0.42, p=0.002).[48] Their study was followed by the PINT study, an RCT by Kirpalani et. al. published in 2006. They focused on ELBW (<1000 grams at birth) infants and enrolled 451 subjects. Their restrictive threshold for capillary Hb ranged from 7.5 to 11.5 g/dL and the liberal was 8.5 to 13.5 g/dL. The short-term results of this larger trial did not show outcome differences between threshold approaches, suggesting that neonates could tolerate anemia better than what we were allowing.[11] But in 2009 the same group of authors published a follow up on the same

cohort that raised concerns for increased occurrences of neurosensory impairment (29% vs. 22%, p=0.07) and cognitive delay (24% vs. 18%, p=0.06) in the restrictive threshold patients.[22] These trials were instrumental in establishing our institutional recommendations, where we used the thresholds established in the liberal strategy from the PINT study.

The other landmark trial for the use of hemoglobin thresholds in RBC transfusions was the TRIPICU study. This was published by Lacroix and colleagues in 2007 and included 637 critically ill children from multiple institutions around the world. They enrolled subjects from 3 days of age to 14 years but their average patient age was 3 years old and they only studied 19 patients that were ≤28 days. This questions the generalizability of the findings to neonates. They excluded patients that were bleeding, hemodynamically unstable, had cardiovascular problems or hemolysis among other criteria. Their restrictive threshold was 7 g/dL and the liberal was 9.5 g/dL.[12] There were no differences in any of the outcomes studied and their non-inferiority was re-established in multiple subset analysis in septic, cardiac surgery and general surgical patients.[13,44,45]

Using the evidence reported in these trials, we created institutional recommendations for the use RBCs based on hemoglobin thresholds. These guidelines were crafted by a working group of pediatric, anesthesia and surgical providers. We then introduced a clinician decision support (CDS) logic into our computerized provider order entry (CPOE) system to collect information about transfusions that were ordered outside of the recommended thresholds. (Chapter 3) In this analysis, we sought to evaluate our adherence to these recommendations as well as the

indications that patients have when receiving transfusions when the hemoglobin level is higher than recommended.

METHODS

In the same way as the study reported in Chapter 3, patients were stratified in two groups as the recommendations and CDS prompt varied depending on their age and location.(Table 3.1) Group 1 were those from 0 to 3 months (≤90days) of age or located in the NICU and Group 2 included patients > 3months (>90 days) to 18 years. This "soft" stop only appeared when the pretransfusion hemoglobin was ≥7g/dL on patients > 3 months of age and ≥8.5g/dL in patients 0 to 3 months of age or located in the NICU. Although institutional recommendations included higher hemoglobin levels for neonates with respiratory support, a single trigger of ≥8.5g/dL was used for patients 0 to 3 months of age and "transfusion is compliant with guidelines" was included as one of the choices to transfuse outside of the pre-established institutional recommendations. The pre and post analyses of this CDS addition is reported in Chapter 3. This analysis includes a detailed description of the transfusions occurring in the 14 months after the CDS was implemented.

Data source

Transfusions from August 28, 2013 to October 31, 2014 at the JHBCC were analyzed. We included allogeneic packed red blood cell transfusions in patients that were 0 to 18 years of age at the time of transfusion. Data were obtained in daily reports of transfusions ordered within the

time of evaluation and pre and post-transfusion hemoglobin was extracted from the patient's chart. Other data included in the daily reports were location, ordering provider and service. The indication to transfuse was also reported in patients that were transfused outside of the hemoglobin thresholds included in institutional recommendations.

We excluded intraoperative transfusions as these were ordered through a different CPOE system and recommendations for blood use in these patients respond to different circumstances than the ones outside of the operating room. Patients that were transfused under massive transfusion protocols, on ECMO or had a transplant (solid or bone marrow) were also excluded. Demographic variables and specific characteristics associated with the transfusion order were analyzed including age, sex, volume transfused (ml/kg or units), role of ordering provider (e.g. resident, fellow, nurse practitioner, etc) and location of the patient.

Subset analyses were performed to assess the adherence to transfusion recommendations in cardiac surgery patients (defined as having an ICD9 procedure code between 35.00 and 39.99 as the primary procedure of their hospitalization).

Outcomes

The primary outcome was the proportion of transfusions compliant with hemoglobin-level based recommendations. This was studied for both age groups and for each hospital location (NICU, PICU and regular inpatient floor). Compliant was defined as a transfusion that occurred when the hemoglobin was under the thresholds stated by the recommendations. These are ≤13.5g/dL in

patients 1 to 7 days old, ≤12 g/dL in patients 8 to 14 days and ≤10 g/dL in patients ≥15 days. The recommendations specify lower Hb thresholds for neonates without respiratory support, but we only used the higher thresholds to define compliance. For children >3 months a transfusion was declared compliant if the Hb was <7 g/dL.

Secondary outcomes included the mean pretransfusion and post-transfusion hemoglobin. The mean change in the hemoglobin level resulted from each transfusion was also investigated and analyzed by high or low volume transfusions. Low volume was defined as those orders for ≤10 ml/kg and high was >10 ml/kg. For patients that were transfused in units of PRBCs, the volume was calculated by multiplying the number of units by 350 and dividing the volume by their weight. The mean volume transfused was compared by ordering hospital unit.

In addition to investigating transfusions individually, we analyzed outcomes by patient. We studied the number of patients with all transfusions compliant, number of transfusions per patient and the number of different indications for repeated non-compliant transfusions.

Statistical comparison of normally distributed variables was conducted with t test or ANOVA and chi-square for categorical variables. Statistical analysis was conducted with STATA/MP 15.1 (College Station, TX).

RESULTS

A total of 2,928 transfusions were screened for our analysis. We excluded transfusions in adults (n=153), transfusions in patients on ECMO or VAD (n=597), heart transplant (n=131), liver transplant (n=19), kidney transplant (n=6), bone marrow transplant (n=65) and from an unknown location (n=2). Our final cohort consisted of 1,955 pediatric transfusions of which 1,104 occurred in patients <3 months of age or in the NICU and 851 in patients >3 months of age. (Fig 4.1)

Group 1- Transfusions in patients <3 months of age or in the NICU

The median age at transfusion was 22 days [8-48]. A total of 243 (22.0%) transfusions occurred in patients 0 to 7 days, 181 (16.4%) in neonates 8 to 14 days, 601 (54.4%) in patients 15 to 90 days and 79 (7.2%) in infants >3 months of age that were still in the NICU. More than half of the transfusions were in male babies (594, 53.8%). A significant amount of transfusions were allocated to patients transfused >10 times (n=359, 32.5%). Most transfusions were ordered as 15 ml/kg (n=753, 68.2%) with 10 ml/kg (n=300, 27.2%) as the second most frequent order. There were four transfusions that were ordered as one or two units which may have occurred as an ordering error. The most frequent ordering providers were residents (n=505, 45.7%) and nurse practitioners (n=452, 40.9%). It is important to recognize that the decision to transfuse is not necessarily made by the ordering provider as there were nine transfusions (0.8%) ordered by a medical student. As expected, the majority of transfusions within this age group occurred in the NICU (n=907, 82.2%) with PICU following (n=183, 16.6%) and the occasional transfusions ordered in the regular floor ward (n=14, 1.3%). (Table 4.1)

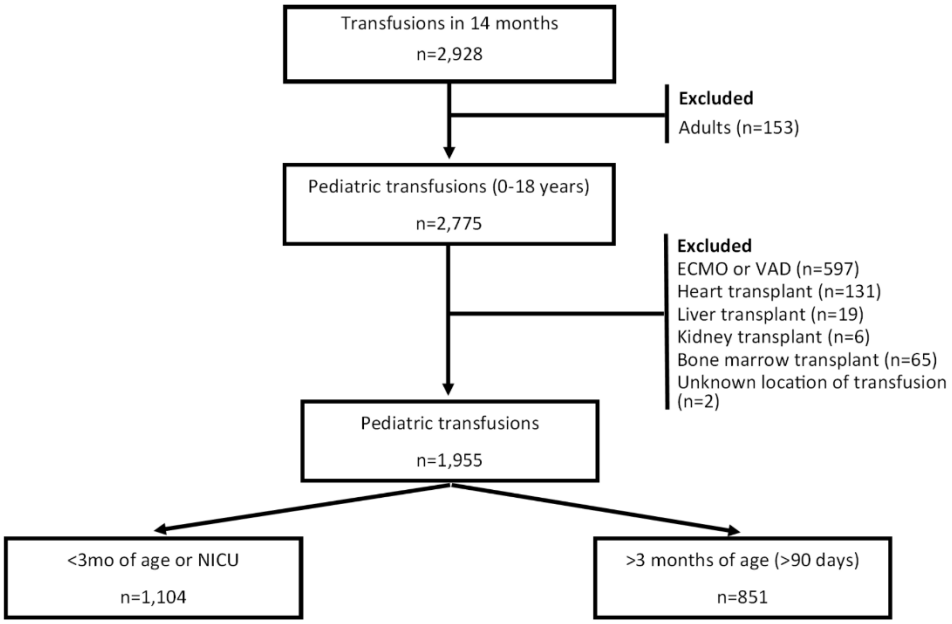

Fig 4.1 Transfusion flow chart and exclusion criteria.
ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

The proportion of compliant transfusion orders varied by hospital location with 386 (42.6%) compliant transfusions in the NICU, 116 (63.4%) in the PICU and 13 (92.9%) in the floor ward ($p<0.001$). (Table 4.2) The hemoglobin thresholds decrease as patients get older and so does the institutional adherence to recommendations. For patients <8 days, 206 transfusions (84.8%) were compliant and this decreased to the point that only 2 (2.5%) transfusions were under recommended thresholds in patients >3 months in the NICU. (Figure 4.2)

A histogram of the pretransfusion Hb was graphed to evaluate for distribution and outliers. The data appeared to be normally distributed without excessive kurtosis. (Figure 4.3) The pretransfusion Hb was significantly different by location. For transfusions in patients 0 to 7 days

Table 4.1. Characteristics of Transfusions and Patients.

	Group 1 <3 months or NICU (n=1,104)	**Group 2** 3 months to 18 years (n=851)
Age, median [IQR]	22 days [8-48]	4 years [1-13]
Age category, n (%)		
0 to 7 days	243 (22.0)	
8 to 14 days	181 (16.4)	
15 to 90 days	601 (54.4)	
3 months to 1 year	79 (7.2)	197 (23.2)
1 to 10 years		367 (43.1)
11 to 18 years		287 (33.7)
Sex, female n(%)	510 (46.2)	398 (46.9)
Transfusions to patients transfused >10 times	359 (32.5)	117 (13.8)
Volume transfused		
<10 ml/kg	35 (3.2)	88 (10.3)
10 ml/kg	300 (27.2)	293 (34.4)
15 ml/kg	753 (68.2)	153 (18.0)
20 ml/kg	12 (1.1)	32 (3.8)
1 unit	2 (0.2)	175 (20.6)
2 units	2 (0.2)	102 (12.0)
Other	0	8 (0.9)
Ordering provider		
Medical Student	9 (0.8)	
Resident	505 (45.7)	462 (54.3)
Fellow	115 (10.4)	256 (30.1)
Attending	12 (1.1)	34 (4.0)
Nurse Practitioner	452 (40.9)	94 (11.1)
Physician Assistant	1 (0.1)	5 (0.6)
Other		
Location		
NICU	907 (82.2)	
PICU	183 (16.6)	569 (66.9)
Acute care ward	14 (1.3)	282 (33.1)

NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

the mean pretransfusion Hb in the NICU was 11.9 ±1.3 g/dL and 12.5 ±2.0 g/dL in the PICU (p=0.026). There were no transfusion orders for patients <15 days old on the floor ward. For neonates 8 to 14 days of age, the mean pretransfusion Hb in the NICU was 11.7 ±1.2 g/dL vs.

11.1 ±2.1 g/dL in the PICU (p=0.041). For patients 15 to 90 days old, the mean pretransfusion Hb in the NICU was 11.0 ±1.4 g/dL, 9.3 ±2.3 in the PICU and 7.2 ±1.2 in the regular floor ward (p<0.001). (Table 4.2)

Table 4.2 Adherence to Guidelines and Hb Levels for Transfusions

	Group 1 < 3 months or older in NICU				**Group 2 3 months to 18 years**		
	NICU n=907	PICU n=183	Floor n=14	*p*	PICU n=569	Floor n=282	*p*
Adherent to guidelines, n(%)	386 (42.6)	116 (63.4)	13 (92.9)	<0.001	158 (27.8)	141 (50.0)	<0.001
Pretransfusion Hb, mean g/dL ±SD							
0 to 7 days	11.9 ±1.3	12.5 ±2.0	n/a	0.026			
8 to 14 days	11.7 ±1.2	11.1 ±2.1	n/a	0.041			
15 to 90 days	11.0 ±1.4	9.3 ±2.3	7.2 ±1.2	<0.001			
3 months to 1y*					10.5 ±1.9	7.0 ±1.6	<0.001
1 to 10 years					8.7 ±3.2	6.8 ±1.3	<0.001
11 to 18 years					7.5 ±1.5	7.4 ±1.3	0.353
Post-transfusion Hb, mean g/dL ±SD							
0 to 7 days	14.3 ±1.8	14.0 ±1.8	n/a	0.3255			
8 to 14 days	14.1 ±1.5	12.9 ±2.4	n/a	<0.001			
15 to 90 days	13.7 ±1.6	11.7 ±2.4	11.8 ±2.7	<0.001			
3 months to 1y*					12.4 ±1.8	10.0 ±2.3	<0.001
1 to 10 years					10.9 ±2.6	9.4 ±1.9	<0.001
11 to 18 years					9.5 ±1.8	9.3 ±1.5	0.331
Change in Hb, mean g/dL ±SD							
0 to 7 days	2.4 ±1.8	1.5 ±1.4	n/a	0.003			
8 to 14 days	2.5 ±1.5	1.8 ±1.4	n/a	0.018			
15 to 90 days	2.8 ±1.6	2.4 ±1.3	4.4 ±2.6	<0.001			
3 months to 1y*					1.9 ±1.7	3.0 ±1.9	0.007
1 to 10 years					2.2 ±1.6	2.6 ±1.5	0.014
11 to 18 years					1.9 ±1.5	1.9 ±1.4	0.816

* the 79 tranfusions that were >3mo and in the NICU were excluded for mean hgb comparisons
NICU, neonatal intensive care unit; PICU, pediatric intenstive care unit; Hb, hemoglobin

The post-transfusion or goal Hb for neonates in the first week of life did not differ by unit. The mean post-transfusion Hb in the NICU was 14.3 ±1.8 g/dL and 14.0 ±1.8 g/dL in the PICU (p=0.3255). For neonates 8 to 14 days of age, the mean post-transfusion Hb in the NICU was 14.1 ±1.5 g/dL vs. 12.9 ±2.4 g/dL in the PICU (p<0.001). For patients 15 to 90 days old, the mean post-transfusion Hb in the NICU was 13.7 ±1.6 g/dL, 11.7 ±2.4 in the PICU and 11.8 ±2.7 in the regular floor ward (p<0.001). (Table 4.2)

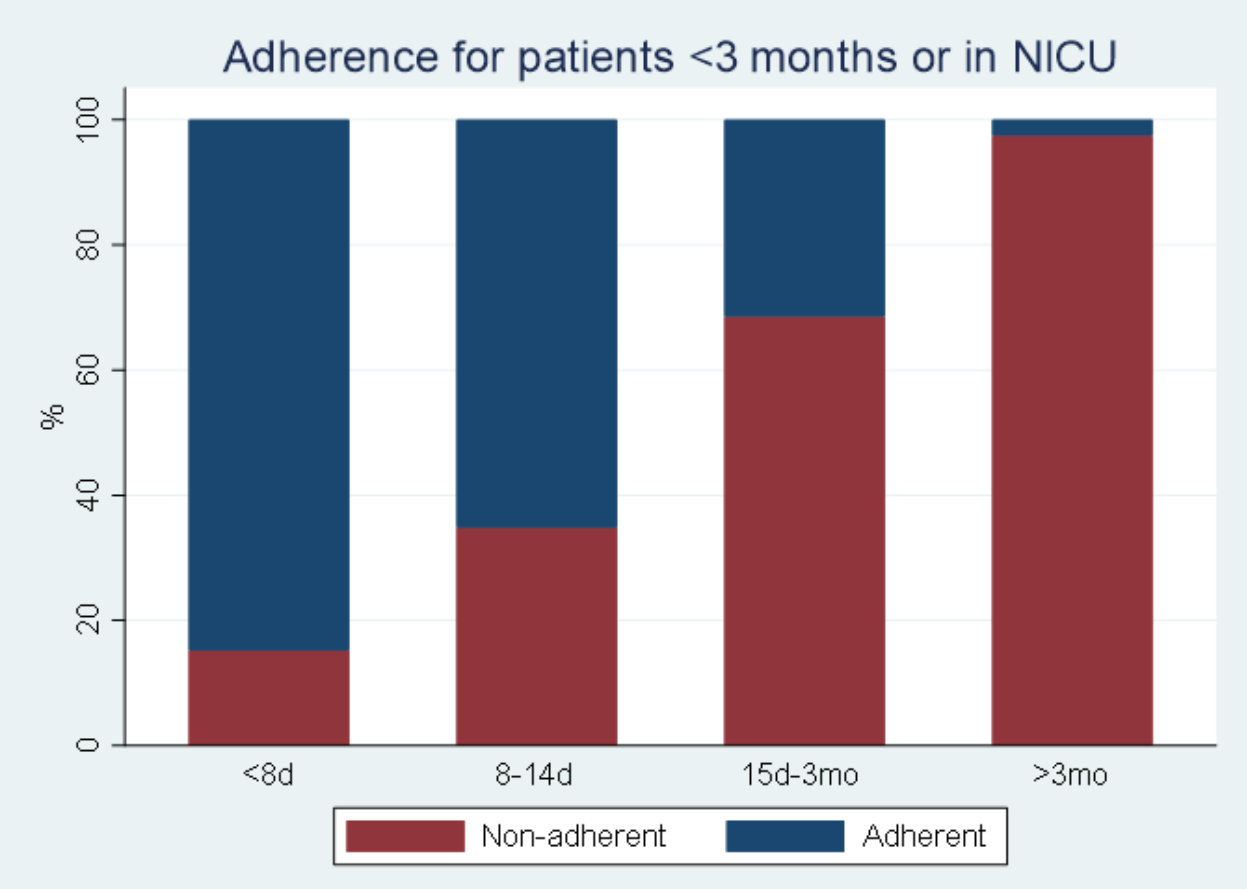

Figure 4.2 Percent adherence to guidelines in patients <3 months of age or in the neonatal intensive care unit by age group.
d, days; mo, months

The change in Hb for patients across almost all age groups was markedly different depending on the ordering unit. The mean change in Hb in the NICU was 2.4 ±1.8 g/dL and 1.5 ±1.4 g/dL in the PICU (p=0.003). For neonates 8 to 14 days of age, the mean change in Hb in the NICU was 2.5 ±1.5 g/dL vs. 1.8 ±1.4 g/dL in the PICU (p=0.018). For patients 15 to 90 days old, the mean change in Hb in the NICU was 2.8 ±1.6 g/dL, 2.4 ±1.3 g/dL in the PICU and 4.4 ±2.6 g/dL in the regular floor ward (p<0.001). (Table 4.2)

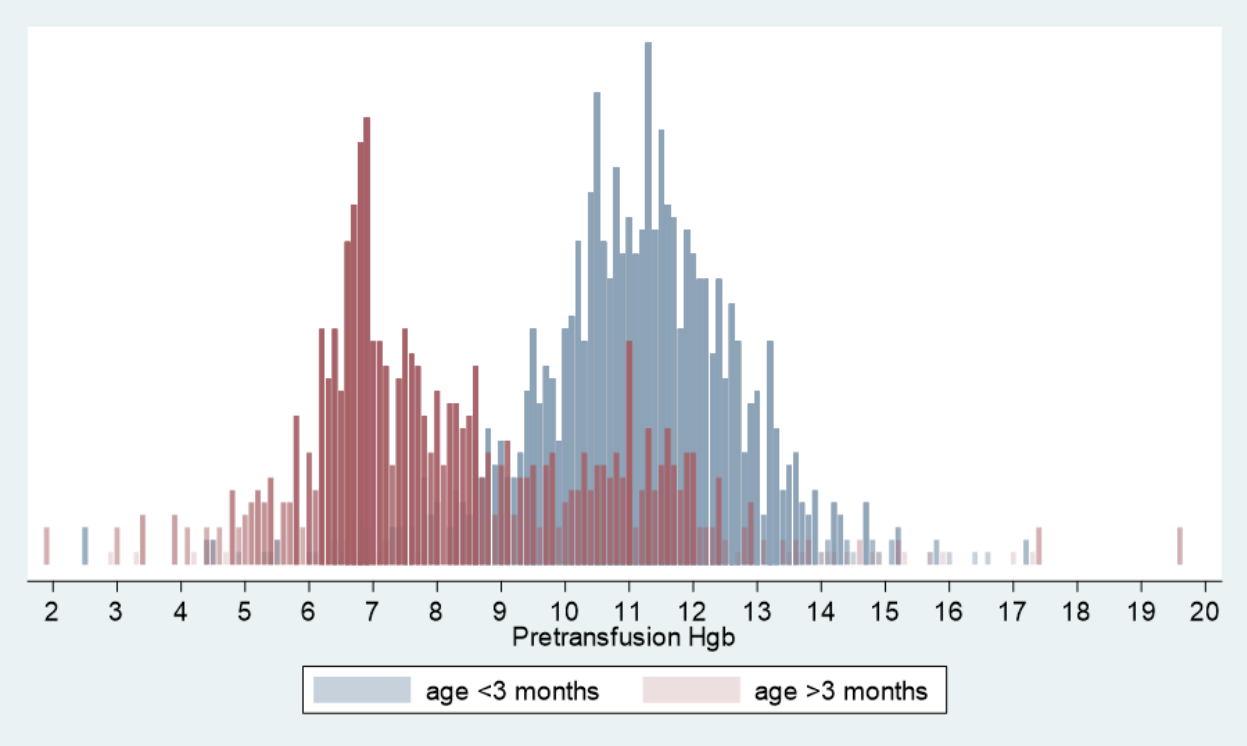

Figure 4.3 Histogram of pretransfusion Hb by age groups. For patients <3 months of age or in the neonatal intensive care unit (blue) there seems to be a normal distribution. For transfusions in patients >3 months (red), there is a bimodal-like distribution with a peak at 7 g/dL and a second peak at 11 g/dL.

The magnitude of the difference in mean change in Hb is concordant with the differences seen in volume ordered by each unit. Patients 0 to 7 days old were transfused 13.8 ±2.4 ml/kg in the

NICU and 9.8 ±3.3 ml/kg in the PICU (p<0.001). Neonates 8 to 14 days old received 13.8 ±2.3 cc/kg in the NICU and 10.0 ±3.7 in the PICU (p<0.001). Infants 15 to 90 days were ordered 14.0 ±2.2 ml/kg in the NICU, 11.0 ±3.2 ml/kg in the PICU and 13.1 ±3.8 in the regular floor ward (p<0.001). (Table 4.3) It is important to note that five transfusions had a significantly high outlier volume due to the fact that they were ordered as full units in small patients. These entries may represent an error in the way the RBCs were ordered therefore we excluded them to allow for improved comparison of mean values. The increase in Hb associated with a low volume transfusion was 2.0 g/dL vs. 3.0 in high volume transfusions (p<0.001) (Figure 4.4.A)

Table 4.3 Volume Characteristics of Transfusions by Age Group and Hospital Location

	Group 1 < 3 months or older in NICU				**Group 2 3 months to 18 years**		
	NICU n=905	PICU n=181	Floor n=14	*p*	PICU n=568	Floor n=282	*p*
Transfusion volume (ml/kg), mean ±SD							
0 to 7 days	13.8 ±2.4	9.8 ±3.3	n/a	<0.001			
8 to 14 days *	13.8 ±2.3	10.0 ±3.7	n/a	<0.001			
15 to 90 days *	14.0 ±2.2	11.0 ±3.2	13.1 ±3.8	<0.001			
3 months to 1 y *					10.4 ±3.0	12.3 ±4.9	0.009
1 to 10 years					11.6 ±5.3	13.4 ±4.9	0.002
11 to 18 years					9.7 ±4.4	10.0 ±4.2	0.519

*5 transfusions were excluded from group 1. These were >100cc/kg (full PRBC units ordered in infants)
NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

Transfusions involving the same patients were also analyzed to report patient-specific outcomes. Since transfusions could occur at different locations throughout the hospital stay of the same patient, we did not report location comparisons. 121 patients (40.2%) in group 1 had all of their

transfusion orders within threshold recommendations. Most of the transfused patients received only one transfusion (n=128, 42.5%) but 27 patients (9.0%) received ≥10 transfusions. For the patients that received at least two transfusions outside of recommended thresholds, only 56 (40.6%) had a consistent indication and 6 patients (4.4%) had more than five indications listed. (Table 4.4)

The most frequent indications to transfuse outside of institutional recommendations were: active cardiac disease (n=58, 9.9%), symptoms attributed to anemia (n=256, 43.5%), transfusion is compliant (n=114, 19.4%), active bleeding (n=56, 9.5%) and "Other" (n=55, 9.3%). Even though the ordering provider used the "transfusion is compliant" option in 267 transfusions, these were not compliant in 114 occasions based on the pretransfusion threshold. (Figure 4.5)

Group 2- Transfusions in patients >3 months of age

The median age at transfusion was 4 years [1-13]. A total of 197 (23.2%) of transfusions occurred in patients 3 months to 1 year, 367 (43.1%) in children 1 to 10 years and 287 (33.7%) in patients 11 to 18 years. More than half of the transfusions were in male children (451, 53.1%). Compared to patients in group 1, a smaller number of transfusions were allocated to patients transfused >10 times (n=117, 13.8%). Different than group 1, transfusions were frequently ordered as 10 ml/kg (n=293, 34.4%) with 1 unit (n=175, 20.6%) as the second most frequent order. The most frequent ordering providers were residents (n=462, 54.3%) and fellows (n=256, 30.1%). The majority of transfusions within this age group occurred in the PICU (n=569, 66.9%) with the rest in the floor ward (n=282, 33.1%). (Table 4.1)

Table 4.4 Transfusion Outcomes by Patient (n=733)

	Group 1 **< 3 months or older in NICU** n=301	**Group 2** **3 months to 18 years** n=432
All transfusions compliant, n(%)	121 (40.2)	151 (35.0)
n of transfusions per patient		
1	128 (42.5)	288 (66.7)
2	49 (16.3)	70 (16.2)
3	28 (9.3)	31 (7.2)
4	18 (6.0)	15 (3.5)
5 to 9	51 (16.9)	20 (4.6)
≥10	27 (9.0)	8 (1.9)
n of different indications for repeated non-compliant transfusions		
same indication	56 (40.6)	67 (57.8)
2	44 (31.9)	37 (31.9)
3	23 (16.7)	9 (7.8)
4	9 (6.5)	1 (0.9)
≥5	6 (4.4)	1 (0.9)

NICU, neonatal intensive care unit.

The proportion of compliant transfusion orders varied by hospital location in this patient group too, with 158 (27.8%) compliant transfusions in the PICU and 141 (50.0%) in the acute care floor ($p<0.001$). (Table 4.2) When analyzed by more detailed age groups, infants 3 months to 1 year had the lowest compliance (n=25, 12.7%) and patients 11 to 18 years the highest (n=122, 42.5%). (Figure 4.6)

A histogram of the pretransfusion Hb was graphed to evaluate for distribution and outliers. The data appeared to be bimodal with the main peak at a hemoglobin level of 7 g/dL and a second smaller peak around 11 g/dL. (Figure 4.3) The pretransfusion Hb was significantly different by location. For transfusions in patients 3 months to 1 year the mean pretransfusion Hb in the PICU

was 10.5 ±1.9 g/dL and 7.0 ±1.6 g/dL in the floor ward ($p<0.001$). For children 1 to 10 years of age, the mean pretransfusion Hb in the PICU was 8.7 ±3.2 g/dL vs. 6.8 ±1.3 g/dL in the acute care ward ($p<0.001$). For patients 11 to 18 years, the mean pretransfusion Hb in the PICU was 7.5 ±1.5 g/dL and 7.4 ±1.3 in the regular floor ward ($p<0.353$). (Table 4.2)

The post-transfusion or goal Hb also differed by unit. For infants 3 months to 1 year, the mean post-transfusion Hb in the PICU was 12.4 ±1.8 g/dL and 10.0 ±2.3 g/dL in the acute care ward ($p<0.001$). For children 1 to 10 years, the mean post-transfusion Hb in the PICU was 10.9 ±2.6 g/dL vs. 9.4 ±1.9 g/dL in the acute care ward ($p<0.001$). For patients 11 to 18 years old, the mean post-transfusion Hb in the PICU was 9.5±1.8 g/dL and 9.3 ±1.5 in the regular floor ward ($p=0.331$). (Table 4.2)

The change in Hb for patients by unit followed a similar pattern than the pre and post-transfusion Hb, it was different for the younger age groups but the same for patients 11 to 18 years of age. The mean change in Hb in the PICU was 1.9 ±1.7 g/dL and 3.0 ±1.9 g/dL in the acute care ward ($p=0.007$). For children 1 to 10 years of age, the mean change in Hb in the PICU was 2.2 ±1.6 g/dL vs. 2.6 ±1.5 g/dL in the floor ward ($p=0.014$). For patients 11 to 18 years old, the mean change in Hb in the PICU was 1.9 ±1.5 g/dL and 1.9 ±1.4 in the regular floor ward ($p=0.816$). (Table 4.2)

As in the case of group 1, there were differences in the mean transfusion volume ordered by unit. For infants 3 months to 1 year in the PICU the mean volume transfused was 10.4 ±3.0 ml/kg and 12.3 ±4.9 ml/kg in the acute care ward (p=0.009). Children 1 to 10 years received 11.6 ±5.3 ml/kg in the PICU and 13.4 ±4.9 ml/kg in the regular floor ward (p=0.002). Patients 11 to 18 years were ordered 9.7 ±4.4 ml/kg in the PICU and 10.0 ±4.2 ml/kg in the regular floor ward (p=0.519). (Table 4.3) The increase in Hb associated with a low volume transfusion was 2.0 g/dL vs. 2.7 in high volume transfusions (p<0.001) (Figure 4.4.B)

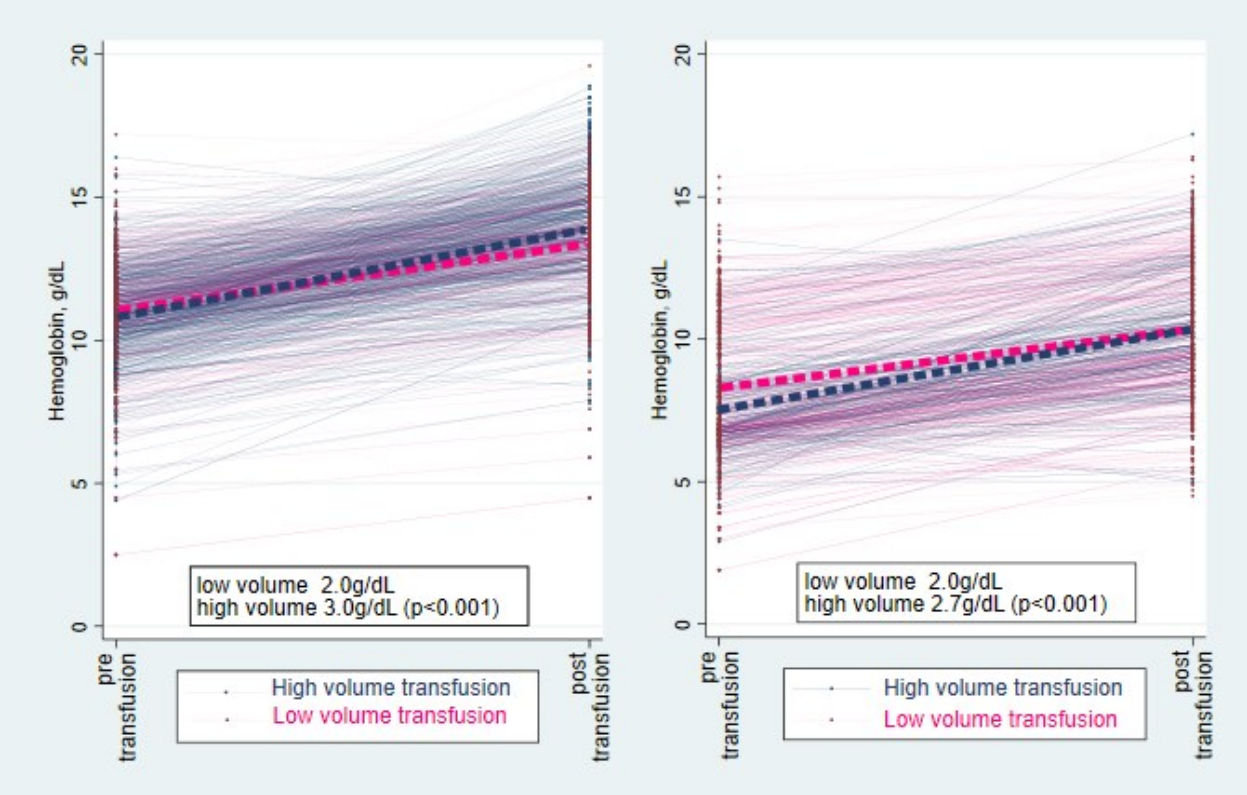

Figure 4.4 Hemoglobin change by transfusion volume. High volume (blue) is >10 ml.kg and low volume (pink) is ≤10 ml/kg. Each line is a transfusion and dotted thick lines are the mean for the volume group. (A) Transfusions in patients <3 months of age or in the neonatal intensive care unit. Mean hemoglobin change for low volume was 2.0 g/dL and for high volume was 3.0 g/dL (p<0.001). (B) Transfusions in patients >3 months of age. Mean hemoglobin change for low volume was 2.0 g/dL and for high volume was 2.7 g/dL (p<0.001)

In group 2 (patients > 3months of age), 151 patients (35.0%) had all of their transfusion orders within threshold recommendations. The majority of transfused patients received only one transfusion (n=288, 66.7%) and 8 patients (1.9%) received ≥10 transfusions. For the patients that received at least two transfusions outside of recommended thresholds, only 67 (57.8%) had a consistent indication. (Table 4.4)

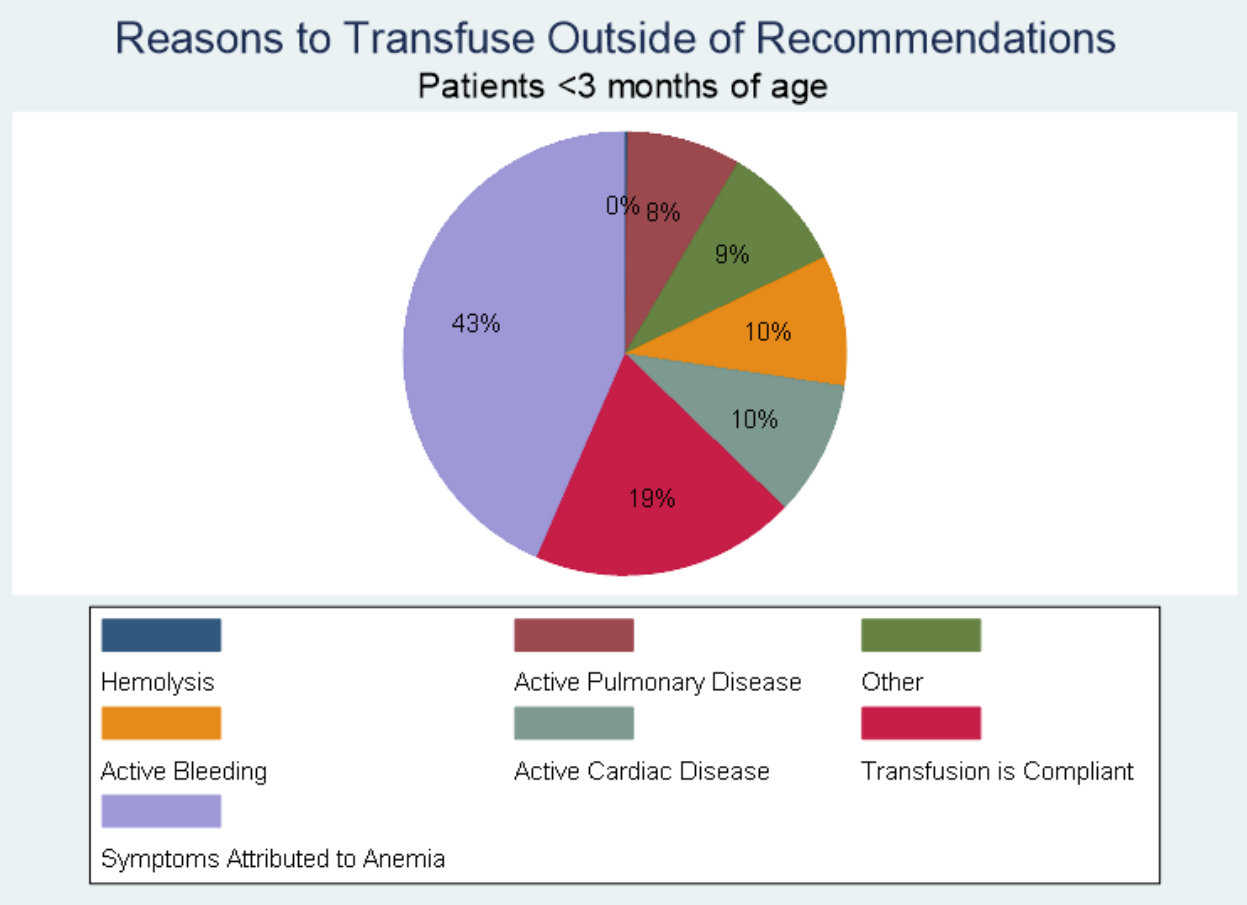

Figure 4.5 Indications to transfuse outside of recommendations for patients <3 months of age or in the neonatal intensive care unit. The reason "Transfusion is Compliant" was checked by the provider but the pretransfusion hemoglobin threshold did not support it.

The most frequent indications to transfuse outside of institutional recommendations were: active bleeding (n=156, 28.3%), active cardiac disease (n=150, 27.2%) and symptoms attributed to anemia (n=110, 19.9%). (Figure 4.7) When focusing on the transfusions that occurred with a pretransfusion Hb >10 g/dL, the majority of them were because of active cardiac disease (n=120, 53.3%)

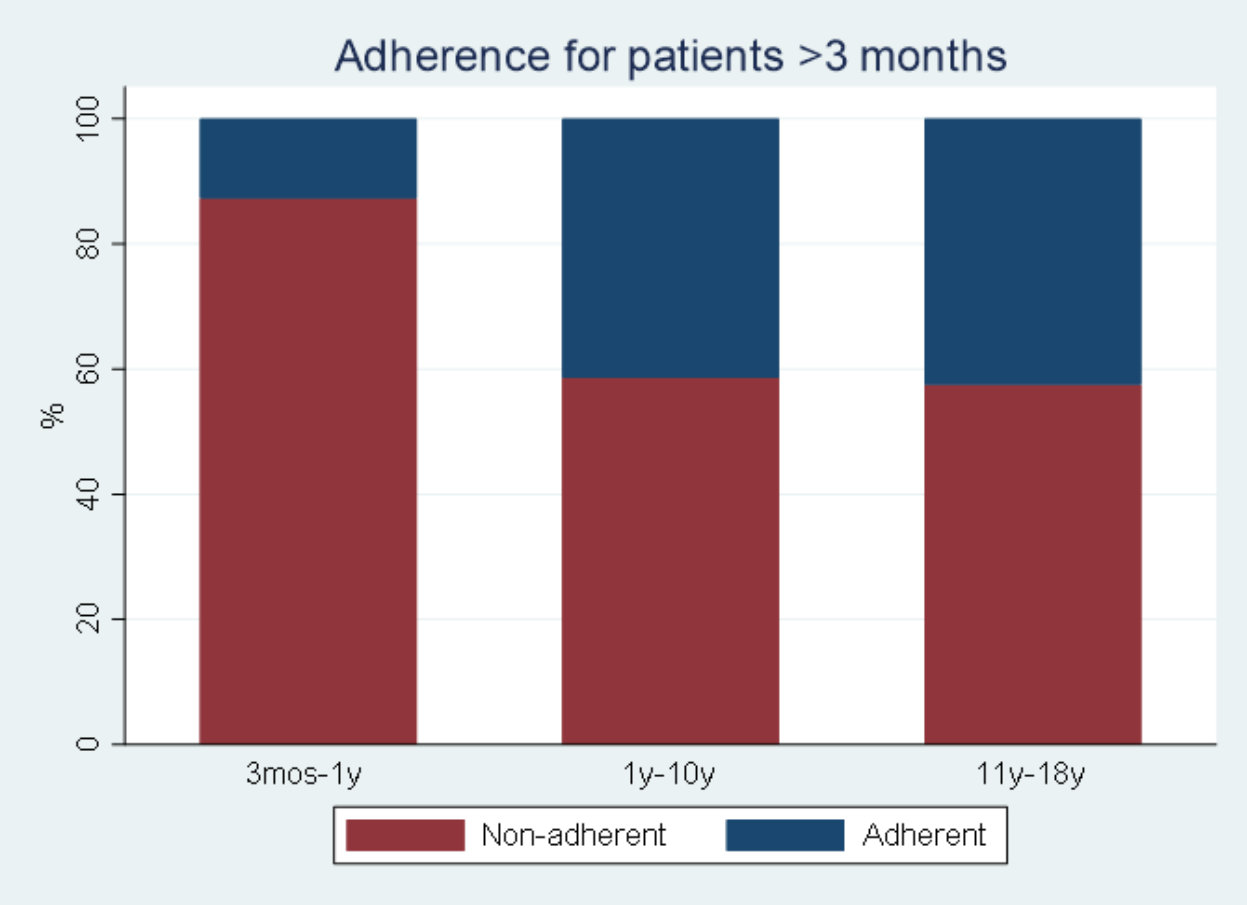

Figure 4.6 Percent adherence to guidelines in patients >3 months of age.
mos, months; y, year/s

Cardiac surgery patients

There were 415 transfusions in patients that underwent a cardiac surgery procedure during their hospital stay. The mean pretransfusion hemoglobin for transfusions in patients with cardiac disease was higher than the rest of the transfusions. For transfusions in infants <3 months of age (n=214) the pretransfusion Hb was 11.3 ±1.6 g/dL, for patients 3 months to 1 year (n=93) was 10.6 ±1.8 g/dL, for children 1 to 10 years (n=74) the pretransfusion Hb was 11.2 ±3.3 g/dL and for the transfusions in patients 11 to 18 years (n=28) the Hb was 8.7 ±1.3 g/dL. The transfusions were compliant with recommendations in only 108 cases (26.0%). (Figure 4.8) The most common indications to transfuse in this population were active cardiac disease (n=110, 35.8%), active bleeding (n=78, 25.4%) and symptoms attributed to anemia (n=65, 21.2%)

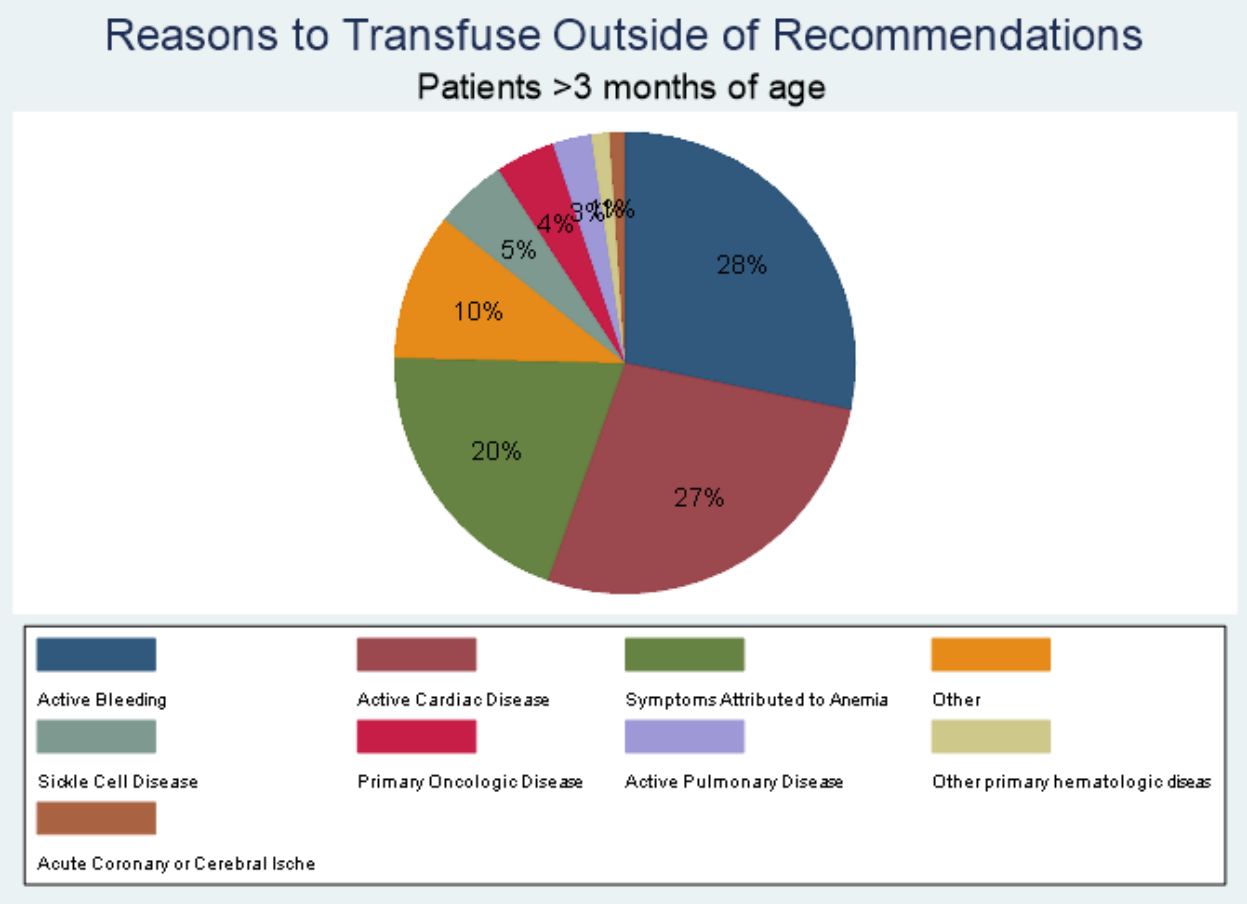

Figure 4.7 Indications to transfuse outside of recommendations for patients >3 months of age.

DISCUSSION

The present analysis shows an institutional report on adherence to hemoglobin-based recommendations for pediatric blood transfusions. For infants less than three months, institutional guidelines suggest a dynamic threshold for transfusion from 8.5 to 13.5 g/dL depending on age and respiratory support. For children > 3 months, our guideline defined a Hb of 7 g/dL to transfuse hemodynamically stable patients without compromise in oxygen delivery. We found that more than half of transfusions at our institution are given above the recommended thresholds and this varied by hospital unit. The most common indications stated by providers were active bleeding and active cardiac disease. In addition, we identified different practices in volume of transfusion depending on the hospital unit were the transfusion was ordered.

Our adherence to guidelines was 46.7% when transfusing patients 0 to 3 months of age and 35.1% in those given to children >3 months. We believe that there are several possible reasons why our adherence was low: (1) a significant amount of patients fell into an exception category within the guidelines (e.g. active bleeding, active cardiac disease); (2) practitioners were hesitant to adhere to guidelines for concerns in the quality of the data supporting them; (3) A Hb threshold of 7 g/dL is low for some congenital heart disease (CHD) patients and our analysis includes these population as there is not a separate cardiac unit at our hospital; (4) there was not enough awareness of the guidelines despite dissemination efforts and CDS logic.

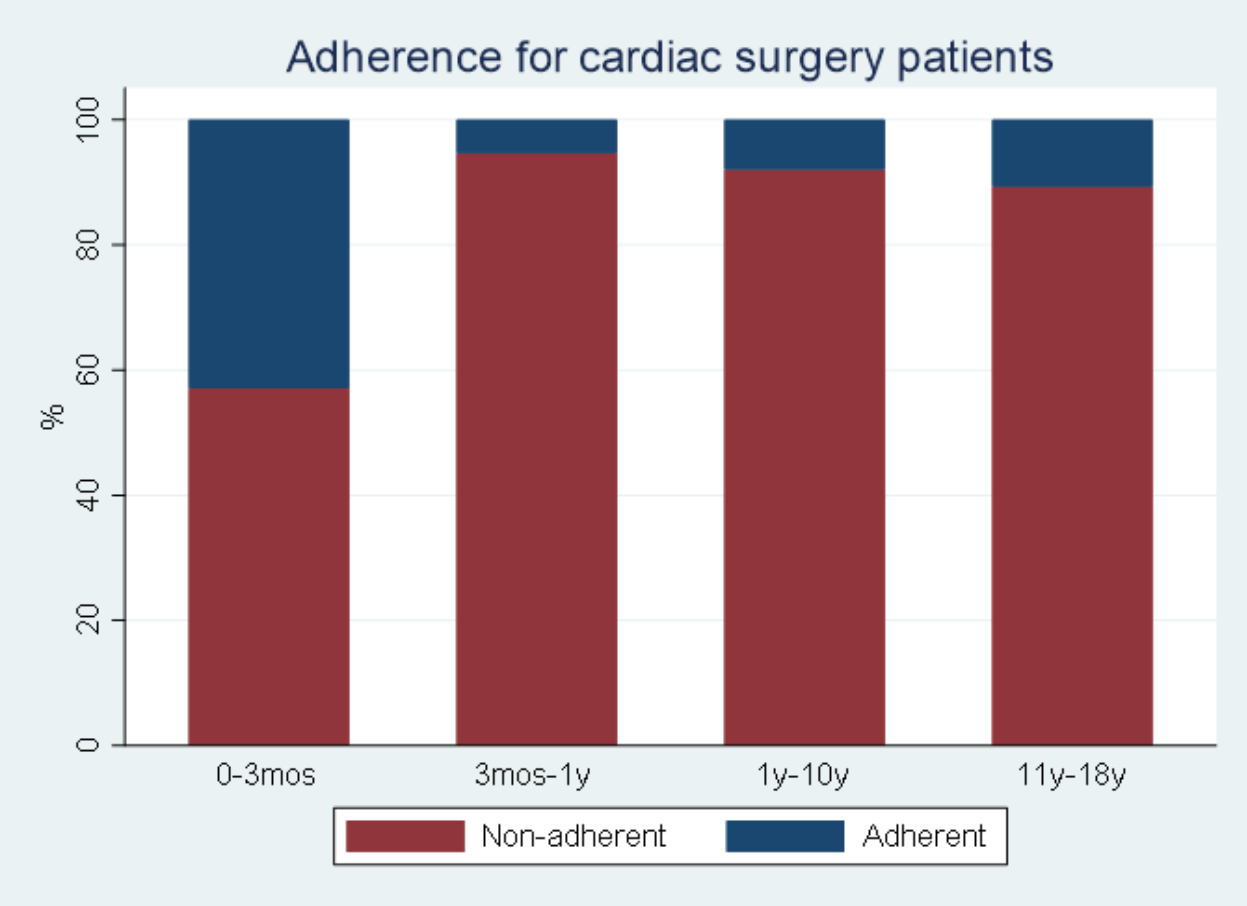

Figure 4.8 Percent adherence to guidelines in cardiac surgery patients.
mos, months; y, year/s

In the case of patients <3 months of age, the low adherence is likely due to lack of strong evidence to support Hb thresholds for transfusion. The PINT study authors reported a trend towards an increased cognitive delay and neurosensory impairment in a follow up report on the patients that were randomized to restrictive Hb tresholds.[22] For this reason, our guidelines for the youngest infants were based on the liberal thresholds of the PINT study. The most common indication to transfuse outside of recommended thresholds was symptomatic anemia (43%). There are two randomized trials currently registered that will offer additional high-quality evidence into the use of thresholds to transfuse premature infants. The Transfusion of Prematures

(TOP) trial has stopped recruiting and the Effects of Transfusion Thresholds on Neurocognitive Outcome of ELBW infants (ETTNO) has been completed but not published yet.[49]

For patients outside of a NICU setting, the evidence behind restrictive Hb thresholds for transfusion is more robust but there are signs that this is still not universally accepted. An international survey of 97 pediatric intensivists by Du Pont-Thibodeau et/al. reported an increase from 1997 to 2010 in the number of physicians who use a threshold of 7 g/dL to consider transfusing a stable critically ill child. Nevertheless, only 8.3% of the respondents reported 7 g/dL as a threshold for a scenario of a patient with septic shock and 16% in a scenario of repaired tetralogy of Fallot.[50] Institutional reports of adherence to pediatric transfusion guidelines are scarce. To our knowledge the only recent study was published in 2019 by Badke et. al. They report that in a 40-bed PICU at a large Children's Center, 53.3% of transfusions were given for a Hb $\leq$7 g/dL.[51] This is higher than our institution possibly due to the fact that they did not include patients in the cardiac care unit and our PICU includes primary cardiac patients.

In 2018, the Pediatric Critical Care Transfusion and anemia Expertise Initiative (TAXI) published a series of extensive recommendations for the use of blood products in pediatric patients.[52,53] Transfusions over a Hb of 7g/dL should be considered for a few indications on hemodynamically stable children. In addition, for patients with cardiac disease, the TAXI group establishes weak recommendations to maintain a Hb between 7-9 g/dL in patients with uncorrected CHD and to avoid transfusion above 9 g/dL in single ventricle patients with adequate oxygenation (for their cardiac lesion) and normal end organ function. For patients with pulmonary hypertension or myocardial dysfunction, there was a consensus in the panel to state

that there is no evidence of a benefit in transfusing above 10 g/dL. In our study, there were 219 transfusions given on patients >3 months when the pretransfusion Hb was >10 g/dL.[54] The main indication for these transfusions was active cardiac disease in 120 occasions (54.8%) and active bleeding in 68 (28.8%). It is important to note that our analysis was performed with transfusions that occurred in 2013 and 2014 and as these data and recommendations become available the number of transfusions with Hb levels this high may be different.

We noticed a significant variability in the ml/kg volume ordered by different units. In patients within the same age group, providers in the NICU, PICU and acute care ward ordered transfusions differently. As an example, in patients 15 to 90 days old, the mean transfusion volume in the NICU was 14.0 ml/kg, in the PICU 11.0 ml/kg and the acute care ward 13.1 ml/kg. While these discrepancies may be explained by variation in disease profiles, they are most likely related to unit-specific practices, where the NICU and floor most commonly order transfusions as 15ml/kg and the PICU does by 10ml/kg. A RCT published by Khodabux and colleagues showed that, while higher volume transfusions lead to less transfusion events in premature neonates, there is no difference in morbidity and long term neurodevelopmental outcomes when using 15cc/kg instead of 20cc/kg.[55,56] An additional concern is that patients receiving >120ml/kg are at risk of developing iron overload and toxicity.[57] One of the main motivations for higher volume transfusions is the potential reduction of donor exposure on premature neonates. This has been addressed at some institutions by establishing single-donor protocols but its implementation is controversial as it leads to the use of RBCs that have been stored for a longer time.[58–60] We stratified transfusions by low (≤10 ml/kg) and high (>10ml/kg) volume and there was a difference in the change in Hb in both age categories (2.1 vs. 3.0 g/dL in infants <3 months and

2.0 vs 2.7 g/dL in children >3 months). Adult literature has supported lower volume transfusions and single-unit transfusion programs have led to more significant decreases in RBC utilization than using restrictive thresholds.[61,62] While further data is needed in premature babies, we believe that adult data is translatable to older children and smaller volumes of transfusion should be preferred.[63]

There are several limitations to our analysis. Our data source was directly extracted from our CPOE system and only transfusions that occurred in inpatient wards are included, therefore patients transfused in the operating room or as an outpatient are missed. In addition, we excluded transplant and extracorporeal life support patients which can account for a significant volume of RBC utilization. While the prescriber was required to select an indication to transfuse out of Hb recommendations, we did not audit their selection and there is a risk that fatigue associated to indication selection made the response inaccurate, a sign of this may be that only 40-60% had a consistent indication when given to the same patient. We did not investigate for physiologic and perfusion parameters around the time of transfusions, therefore we cannot conclude if the adherence rates reported were appropriately low.

CONCLUSION

Randomized trials have shown non-inferiority of restrictive Hb thresholds for RBC transfusions and this has guided the development of institution-specific recommendations as a measure to optimize blood utilization. While this is high-quality evidence, there is a significant number of patients where the results cannot be generalized. At our institution, close to half of the transfusions were given outside of recommended Hb thresholds. The most common indications

were cardiac disease, active bleeding and symptomatic anemia. As hospitals implement guidelines for transfusion practices it is relevant to constantly evaluate institutional adherence and identify populations where unnecessary transfusions may be decreased.

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27. Vélez-Díaz-Pallarés, M., Pérez-Menéndez-Conde, C. & Bermejo-Vicedo, T. Systematic review of computerized prescriber order entry and clinical decision support. *Am. J. Health. Syst. Pharm.* **75**, 1909–1921 (2018).
28. Zuckerberg, G. S. *et al.* Efficacy of education followed by computerized provider order entry with clinician decision support to reduce red blood cell utilization. *Transfusion (Paris)* **55**, 1628–1636 (2015).
29. Adams, E. S. *et al.* Computerized physician order entry with decision support decreases blood transfusions in children. *Pediatrics* **127**, e1112-9 (2011).
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31. Salazar, J. H. *et al.* Regionalization of Pediatric Surgery: Trends Already Underway. *Ann. Surg.* **263**, 1062–1066 (2016).
32. Akaike, H. A new look at the statistical model identification. *IEEE Trans. Autom. Control* **19**, 716–723 (1974).
33. Petäjä, J., Andersson, S. & Syrjälä, M. A simple automatized audit system for following and managing practices of platelet and plasma transfusions in a neonatal intensive care unit. *Transfus. Med.* **14**, 281–288 (2004).

34. McCrory, M. C., Strouse, J. J., Takemoto, C. M. & Easley, R. B. Computerized Physician Order Entry Improves Compliance With a Manual Exchange Transfusion Protocol in the Pediatric Intensive Care Unit: *J. Pediatr. Hematol. Oncol.* **36**, 143–147 (2014).
35. Bembea, M. M. *et al.* Recommendations on the Indications for RBC Transfusion for the Critically Ill Child Receiving Support From Extracorporeal Membrane Oxygenation, Ventricular Assist, and Renal Replacement Therapy Devices From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative: *Pediatr. Crit. Care Med.* **19**, S157–S162 (2018).
36. Steiner, M. E. *et al.* Recommendations on RBC Transfusion Support in Children With Hematologic and Oncologic Diagnoses From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative: *Pediatr. Crit. Care Med.* **19**, S149–S156 (2018).
37. Hibbs, S. P. *et al.* The Impact of Electronic Decision Support on Transfusion Practice: A Systematic Review. *Transfus. Med. Rev.* **29**, 14–23 (2015).
38. Shander, A. *et al.* Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion (Paris)* **50**, 753–65 (2010).
39. Hardin, J. W. & Hilbe, J. M. Regression Models for Count Data Based on the Negative Binomial(p) Distribution. *Stata J. Promot. Commun. Stat. Stata* **14**, 280–291 (2014).
40. Khan, A., Ullah, S. & Nitz, J. Statistical modelling of falls count data with excess zeros. *Inj. Prev.* **17**, 266–270 (2011).
41. Grimm, K. J. & Stegmann, G. Modeling change trajectories with count and zero-inflated outcomes: Challenges and recommendations. *Addict. Behav.* (2018). doi:10.1016/j.addbeh.2018.09.016

42. Howarth, C., Banerjee, J. & Aladangady, N. Red Blood Cell Transfusion in Preterm Infants: Current Evidence and Controversies. *Neonatology* **114**, 7–16 (2018).
43. Guillen, U. *et al.* International survey of transfusion practices for extremely premature infants. *Semin Perinatol* **36**, 244–7 (2012).
44. Willems, A. *et al.* Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: a subgroup analysis. *Crit Care Med* **38**, 649–56 (2010).
45. Karam, O. *et al.* Red blood cell transfusion thresholds in pediatric patients with sepsis. *Pediatr Crit Care Med* **12**, 512–8 (2011).
46. Doctor, A. *et al.* Recommendations on RBC Transfusion in General Critically Ill Children Based on Hemoglobin and/or Physiologic Thresholds From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative: *Pediatr. Crit. Care Med.* **19**, S98–S113 (2018).
47. New, H. V. *et al.* Red blood cell transfusion practice in children: current status and areas for improvement? A study of the use of red blood cell transfusions in children and infants. *Transfusion (Paris)* **54**, 119–127 (2014).
48. Bell, E. F. *et al.* Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics* **115**, 1685–91 (2005).
49. The 'Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO)' Study: Background, Aims, and Study Protocol. *Neonatology* **101**, 301–305 (2012).
50. Du Pont-Thibodeau, G., Tucci, M., Ducruet, T. & Lacroix, J. Survey on Stated Transfusion Practices in PICUs*: *Pediatr. Crit. Care Med.* **15**, 409–416 (2014).

51. Badke, C. M., Borrowman, J. A., Haymond, S., Rychlik, K. & Malakooti, M. R. 7 Is the New 8: Improving Adherence to Restrictive PRBC Transfusions in the Pediatric ICU. *J. Healthc. Qual.* 1 (2019). doi:10.1097/JHQ.0000000000000176

52. Bembea, M. M. *et al.* The Pediatric Critical Care Transfusion and Anemia Expertise Initiative Consensus Conference Methodology: *Pediatr. Crit. Care Med.* **19**, S93–S97 (2018).

53. Valentine, S. L. *et al.* Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative: *Pediatr. Crit. Care Med.* **19**, 884–898 (2018).

54. Cholette, J. M., Willems, A., Valentine, S. L., Bateman, S. T. & Schwartz, S. M. Recommendations on RBC Transfusion in Infants and Children With Acquired and Congenital Heart Disease From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative: *Pediatr. Crit. Care Med.* **19**, S137–S148 (2018).

55. Khodabux, C. M. *et al.* A comparative cohort study on transfusion practice and outcome in two Dutch tertiary neonatal centres. *Transfus. Med.* **19**, 195–201 (2009).

56. von Lindern, J. S. *et al.* Long-term outcome in relationship to neonatal transfusion volume in extremely premature infants: a comparative cohort study. *BMC Pediatr* **11**, 48 (2011).

57. Treviño-Báez, J. D., Briones-Lara, E., Alamillo-Velázquez, J. & Martínez-Moreno, M. I. Multiple red blood cell transfusions and iron overload in very low birthweight infants. *Vox Sang.* **112**, 453–458 (2017).

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59. Strauss, R. G. Controversies in the Management of the Anemia of Prematurity Using Single-Donor Red Blood Cell Transfusions and/or Recombinant Human Erythropoietin. *Transfus. Med. Rev.* **20**, 34–44 (2006).
60. Dollat, C. *et al.* Protocole donneur unique : pratiques transfusionnelles et facteurs de risque des transfusions multiples en réanimation néonatale. *Arch. Pédiatrie* **23**, 935–943 (2016).
61. Podlasek, S. J. *et al.* Implementing a "Why give 2 when 1 will do?" Choosing Wisely campaign. *Transfusion (Paris)* **56**, 2164–2164 (2016).
62. Callum, J. L., Waters, J. H., Shaz, B. H., Sloan, S. R. & Murphy, M. F. The AABB recommendations for the Choosing Wisely campaign of the American Board of Internal Medicine. *Transfusion (Paris)* **54**, 2344–2352 (2014).
63. Thakkar, R., Podlasek, S., Rotello, L., Ness, P. & Frank, S. Two-Unit Red Cell Transfusions in Stable Anemic Patients. *J. Hosp. Med.* **12**, 747–749 (2017).

Curriculum Vitae

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Contact Information

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Languages: English (100%)
Spanish (100%, native)
Place of Birth: Monterrey, Mexico
Date of Birth: May 10, 1983

Education

Medical School
Escuela de Medicina del Tec de Monterrey
Instituto Tecnológico de Estudios Superiores de Monterrey (ITESM)
August 2001 to February 2008
Monterrey, Mexico

Post Graduate Education and Training

Post-Doctoral Research Fellow
Division of Pediatric Surgery, Johns Hopkins School of Medicine
Mentor: Fizan Abdullah, M.D., Ph.D.
March 2009 to March 2010
July 2012 to June 2014
Baltimore, MD, USA

Preliminary Resident in General Surgery
Johns Hopkins Hospital, Johns Hopkins School of Medicine
Program Director: Pamela Lipsett, M.D., M.H.P.E.

July 2010 to June 2012
Baltimore, MD, USA

PhD in Clinical Investigation- Candidate
Bloomberg School of Public Health, Johns Hopkins University
Academic Advisor: Dorry Segev, M.D., Ph.D.
September 2012 to present
Baltimore, MD, USA

Resident in General Surgery
University of Maryland Medical Center, University of Maryland
Program Director: Stephen Kavic, M.D.
July 2014 to June 2017
Baltimore, MD, USA

Surgical Critical Care Fellow, Pediatric track
Children's Hospital of Wisconsin, Medical College of Wisconsin
Program Director: Panna Codner, MD & Marjorie Arca, MD
July 2017 to June 2018
Milwaukee, WI, USA

Post-Doctoral Research Fellow
Division of Pediatric Surgery, Medical College of Wisconsin
Mentor: Dave Lal, MD
July 2018 to July 2019
Milwaukee, WI, USA

Pediatric Surgery Fellow
Children's Hospital of Wisconsin, Medical College of Wisconsin
Program Director: Casey Calkins, MD
August 2019 to July 2021
Milwaukee, WI, USA

Certifications

Educational Commission for Foreign Medical Graduates (ECFMG)
Issued: July 2009

DEA registration

Issued: October 2013
Expiration: February 2019

Advanced Trauma Life Support (ATLS)
Issued: October 2012
Expiration: April 14, 2021

Medical Licensures

Maryland's Physician License
Issued: September 2012
Expiration: September 2017

Wisconsin's Physician License
Issued: November 2016
Expiration: October 2019

Employment History

Medical Community Service
San Rafael Health Clinic
National Health Department, Mexico
February 2007 to February 2008
Ciudad Valles, San Luis Potosí, Mexico

Professional Society Memberships/Participation

Resident Member, American College of Surgeons. *2010 to present*
Resident Member, American Pediatric Surgical Association, *2014 to present*
Member, Association for Academic Surgery. *2017 to present*
Member, International Pediatric Endosurgery Group, *2019 to present*

Committee Participation

Resident Member, Practice Committee, American Pediatric Surgical Association, *September 2015 to September 2018*

Resident Member, Transfusion Practices, University of Maryland Medical Center, *March 2016 to June 2017*

Invited Lectures, Seminars and Academic Events

Judge, Medical Student Poster Session, American College of Surgeons Clinical Congress, Chicago IL, *October 2015*.
Panel Member, Residency Panel, Northeast Regional Conference for the Latino Medical Student Association, Baltimore, MD, *21 Feb 2015*.

Courses

Health Science Research Methods. American College of Surgeons. December 6-8, 2018. Chicago, IL

Honors and Awards

Surgical Intern Colleague Award, *May 2011. Johns Hopkins Nursing*
Resident Teaching Award, *June 2017. University of Maryland General Surgery Residency Program*

Clinical Activities

Moonlight/Hospital Credentialing:

Senior Resident call
General Pediatric Surgery Service, Johns Hopkins Hospital
Four calls a month
July 2012 – June 2014

Intern call
Surgery Service, Mercy Hospital
Three calls a month
February 2014- June 2014

Surgical Assistant call

Surgical Services, LifeBridge Health- Northwest Hospital
Four calls a month
May 2014 – July 2014

Administrative Service

Student Association President
Escuela de Medicina del Tec de Monterrey
Instituto Tecnológico de Estudios Superiores de Monterrey (ITESM)
June 2004 to June 2005
Monterrey, Mexico

Ad Hoc Reviewer

Journal of the American College of Surgeons
Surgery
Pediatrics

Grant Support

Federal Scholarship for PhD studies, Mexican Council for Science and Technology. Support for PhD studies and associated research.
USD$ 82,558
August 2013 to May 2015

Publications

Peer-reviewed publications

1. Rhee D, Zhang Y, Chang DC, Arnold MA, **Salazar-Osuna JH**, Chrouser K, Colombani PM, Abdullah F. Population-based comparison of open vs laparoscopic esophagogastric fundoplication in children: application of the AHRQ pediatric quality indicators. J Pediatr Surg. 2011 Apr;46(4):648-54
2. Chang DC, **Salazar-Osuna JH,** Choo SS, Arnold MA, Colombani PM, Abdullah F. Benchmarking the quality of care of infants with low-risk gastroschisis using a novel risk stratification index. Surgery. 2010 Jun;147(6):766-71

3. Choo S, Papandria D, Zhang Y, Camp M, **Salazar JH**, Scholz S, Rhee D, Chang D, Abdullah F. Outcomes analysis after percutaneous abdominal drainage and exploratory laparotomy for necrotizing enterocolitis in 4,657 infants. Pediatr Surg Int. 2011 Jul;27(7):747-53
4. Chang DC, Rhee DS, Zhang Y, **Salazar JH**, Chrouser K, Choo S, Colombani PM, Abdullah F. Evaluating metrics for quality: death on the same day of elective pediatric surgery. Am J Med Qual. 2012 May-Jun;27(3):195-200.
5. Papandria D, Goldstein SD, Rhee D, **Salazar JH**, Arlikar J, Gorgy A, Ortega G, Zhang Y, Abdullah F. Risk of perforation increases with delay in recognition and surgery for acute appendicitis. J Surg Res. 2013 Oct;184(2):723-9
6. Papandria D, Arlikar J, Sacco Casamassima MG, Ortega G, **Salazar JH**, Zhang Y, Lukish J, Colombani P, Abdullah F. Increasing age at time of pectus excavatum repair in children: Emerging consensus? J Pediatr Surg. 2013. Jan;48(1):191-6
7. Rhee D, **Salazar JH**, Zhang Y, Yang J, Yang J, Papandria D, Ortega G, Goldin AB, Rangel SJ, Chrouser K, Chang DC, Abdullah F. A novel multispecialty surgical risk score for children. Pediatrics. 2013 Mar;131(3):e829-36
8. Casamassima MGS, **Salazar JH**, Papandria D, Fackler J, Chrouser K, Boss EF, Abdullah F. Use of risk stratification indices to predict mortality in critically ill children. Eur J Pediatr. 2014 Jan;173(1);1-13
9. Garonzik-Wang JM, Brat G, **Salazar JH**, Dhanasopon A, Lin A, Akinkuotu A, O'Daly A, Elder B, Olingo K, Burns W, Camp M, Lipsett PA, Freischlag JA, Haut ER. Missing consent forms in the preoperative area: a single-center assessment of the scope of the problem and its downstream effects. JAMA Surg. 2013 Sep;148(9):886-9.
10. Casamassima MGS, Goldstein SD, **Salazar JH**, McIltrot KH, Abdullah F, Colombani PM. Perioperative strategies and technical modifications to the Nuss repair for pectus excavatum in pediatric patients: a large volume, single institution experience. J Pediatr Surg. 2014 Apr;49(4):575-82.
11. Casamassima MGS, Goldstein SD, **Salazar JH**, Papandria D, McIltrot KH, O'Neill DE, Abdullah F, Colombani PM. Operative management of acquired Jeune's syndrome. J Pediatr Surg. 2014 Jan;49(1):55-60
12.Salazar JH, Goldstein SD, Yang J, Douaiher J, Al-Omar K, Michailidou M, Aboagye J, Abdullah F. Regionalization of the surgical care of children: A risk-adjusted comparison of hospital surgical outcomes by geographic areas. Surgery. 2014 Aug;156(2), 467-474.
13.Salazar JH, Yang J, Shen L, Abdullah F, Kim TW. Pediatric Malignant Hyperthermia: Risk Factors, Morbidity and Mortality Identified from the Nationwide Inpatient Sample and Kids' Inpatient Database. Paediatr Anaesth.

2014 Dec;24(12):1212-6.
14. **Salazar JH,** Gabre-Kidan A, Ortega G, Scorpio D, Oldenburg G, Custis H, Ruben D, Albano M, Choo SS, Rhee DS, Fulton WB, Crino JP, Abdullah F. Extracorporeal fetal support: a new animal model with preservation of the placenta. J Pediatr Surg. 2014 Oct;49(10), 1441-1445.
15. Van Arendonk KJ, Goldstein SD, **Salazar JH,** Kumar K, Lau HT, Colombani PM. A nipple-valve technique for ureteroneocystostomy in pediatric kidney transplantation. Pediatr Transplant. 2015 Feb;19(1):42-7.
16. Michailidou M, Goldstein SD, **Salazar J,** Aboagye J, Stewart D, Efron D, Abdullah F, Haut ER. Helicopter overtriage in pediatric trauma. J Pediatr Surg. 2014 Nov;49(11):1673-7.
17. Fox N, Schwartz D, **Salazar JH**, Haut ER, Dahm P, Black JH, Brakenridge SC, Como JJ, Hendershot K, King DR, Maung AA, Moorman ML, Nagy K, Petrey LB, Tesoriero R, Scalea TM, Fabian TC. Evaluation and management of blunt traumatic aortic injury: A practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2015 Jan;78(1):136-46.
18. Goldstein SD, Culbertson NT, Garrett D, **Salazar JH,** Van Arendonk K, McIltrot K, Felix M, Abdullah F, Crawford T, Colombani P. Thymectomy for myasthenia gravis in children: A comparison of open and thoracoscopic approaches. J Pediatr Surg. 2015 Jan;50(1):92-7.
19. Papandria D, Goldstein SD, **Salazar JH**, Cox JT, McIltrot K, Stewart FD, Arnold M, Abdullah F, Colombani P. A randomized trial of laparoscopic versus open Nissen fundoplication in children under two years of age. J Pediatr Surg. 2015 Feb;50(2):267-71.
20. Michailidou M, Sacco Casamassima MG, Karim O, Gause C, **Salazar JH**, Goldstein SD, Abdullah F. Diagnostic imaging for acute appendicitis: interfacility differences in practice patterns. Pediatr Surg Int. 2015 Apr;31(4):355-61.
21. Goldstein SD, Van Arendonk K, Aboagye JK, **Salazar JH**, MIchailidou M, Ziegfeld S, Lukish J, Stewart FD, Haut ER, Abdullah F. Secondary overtriage in pediatric trauma: can unnecessary patient transfers be avoided? J Pediatr Surg. 2015 Jun;50(6):1028-31.
22. Goldstein SD, Pryor H, **Salazar JH**, Dalesio N, Steweart FD, Abdullah F, Colombani P, Lukish JR. Ultrasound-Guided percutaneous central venous access in low birth weight infants: feasibility in the smallest of patients. J Laparoendosc Adv Surg Tech A. 2015 Sep;25(9):767-9.
23. Michailidou M, Sacco Casamassima MG, Goldstein SD, Gause C, Karim O, **Salazar JH**, Yang J, Abdullah F. The impact of obesity on laparascopic

appendectomy: Results from the ACS National Surgical Quality Improvement Program pediatric database. J Pediatr Surg. 2015 Nov;50(11):1880-4.

24. Michailidou M, Goldstein SD, Sacco Casamassima MG, **Salazar JH**, Elliott R, Hundt J, Abdullah F. Laparoscopic versus open appendectomy in children: the effect of surgical technique on healthcare costs. Am J Surg. 2015 Aug;210(2):270-5.

25. Klaus SA, Frank SM, **Salazar JH**, Cooper S, Beard L, Abdullah F, Fackler JC, Heitmiller ES, Ness PM, Resar LM. Hemoglobin thresholds for transfusion in pediatric patients at a large academic health center. Transfusion. 2015 Dec;55(12):2890-7.

26. Abdullah F, **Salazar JH**, Gause CD, Gadepalli S, Biester TW, Azarow KS, Brandt ML, Chung DH, Lund DP, Rescorla FJ, Waldhausen JH, Tracy TF, Fallat ME, Klein MD, Lewis FR, Hirschl RB. Understanding the Operative Experience of the Practicing Pediatric Surgeon: Implications for Training and Maintaining Competency. JAMA Surg. 2016 Aug 1;151(8):735-41.

27. **Salazar JH**, Goldstein SD, Yang J, Gause C, Swarup A, Hsiung GE, Rangel SJ, Goldin AB, Abdullah F. Regionalization of Pediatric Surgery: Trends Already Underway. Annals of Surgery. 2016 Jun;263(6):1062-6.

28. Gause CD, Casamassima MG, Yang J, Hsiung G, Rhee D, **Salazar JH**, Papandria D, Pryor HI 2nd, Steward D, Lukish J, Colombani P, Chandler NM, Johnson E, Abdullah F. Laparoscopic versus open inguinal hernia repair in children <3: a randomized controlled trial. Pedatr Surg Int. 2017 Mar;33(3):367-376.

29. Kalsi R, Drucker CB, **Salazar JH**, Luther LI, Diaz JJ, Kundi RR. Blunt multifocal aortic injury with abdominal aortic intimointimal intussusception. J Vasc Surg. 2018 Feb 24;4(1):37-40

30. Landisch RM, Loomba RS, **Salazar JH**, Buelow MW, Frommelt M, Anderson RH, Wagner AJ. Is isomerism a risk factor for intestinal volvulus? J Pediatr Surg. 2018 Jun;53(6):1118-1122

Books

Contributing author. The Johns Hopkins ABSITE Review Manual, Editors: Meguid, R.A., Van Arendonk, K.J. and Lipsett, P.A. 2nd Edition. Philadelphia: Lippincott, Wiliiams and Wilkins, 2013. ISBN-13 978-1451173321.

Presentations

Salazar JH. A new animal model of extracorporeal fetal support with preservation of the placenta. Innovation Session. American Pediatric Surgical Association. Palm Desert, CA. May 2011

Salazar JH, Abdullah F. Improved outcomes in patients with gastroschisis: Advances in surgery and critical care. Academic Surgical Congress. New Orleans, LA. Feb 2013

Salazar JH. Regionalization of the Surgical Care of Children: A Risk-Adjusted Comparison of Hospital Surgical Outcomes by Geographic Markets. Academic Surgical Congress. San Diego, CA. Feb 2014

Salazar JH. Regionalization of Pediatric Surgery: Trends Already Underway. American Academy of Pediatrics Surgical Section. San Diego, CA. Oct 2014.

Salazar JH. Characterization of perioperative blood transfusion rates in pediatric surgery. Pacific Association of Pediatric Surgeons. Sapporo, Japan. May 2018.

Salazar JH. A simple and effective laparoscopic technique for antegrade enemas. International Pediatric Endosurgery Group. Santiago, Chile. March 2019.